

Methodological issues in nonpharmacological trials for chronic pain

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Nonpharmacological interventions for chronic pain are commonly used in clinical practice, even though some practitioners may not recognize them as true interventions. Establishing reliable evidence of efficacy and effectiveness can be challenging in terms of the design or interpretation of studies of nonpharmacological interventions. This issue of *Pain: Clinical Updates* will describe some of the more important and unique methodological issues pertaining to clinical trials of nonpharmacological interventions.

(Bennett MI, Closs SJ. Methodological issues in nonpharmacological trials for chronic pain. *Anaesth Pain & Intensive Care* 2010;14(1):49-55.)

NONPHARMACOLOGICAL INTERVENTIONS IN PRACTICE

DEFINING A NONPHARMACOLOGICAL INTERVENTION

A useful starting point is to define terms. An intervention defined as “coming between” or “the act of intervening,”¹ and “nonpharmacological” means any approach that is not pharmacological. It is always hard to define (and therefore understand) what something is not rather than what it is. These definitions suggest that we are examining some action or behavior that is not drug based and that “comes between” the pathophysiological mechanism of the chronic pain and the patient’s perception of that pain. According to this concept, examples of nonpharmacological interventions are broad ranging and can be loosely grouped as oriented towards physical, psychological, or clinical process aspects of care (Table 1). However, the table is not an exhaustive list of every type of intervention. There may also be sociological or cultural influences; pharmacological interventions are usually associated with physicians, whereas nonpharmacological interventions are usually associated with nursing practice or other nonphysicians (physiotherapists, psychologists, chiropractors, etc.).² This division (real or perceived) seems unhelpful, especially if it results in nonpharmacological interventions being perceived as less valuable or less effective than pharmacological approaches. The paradox is that the opposite can be true, especially in chronic noncancer pain contexts.

STUDIES OF NONPHARMACOLOGICAL INTERVENTIONS IN CHRONIC PAIN

Even though clinical trials of nonpharmacological

interventions are easily found in the literature, these interventions can be overshadowed by pharmacological interventions in management pathways for patients with chronic pain. Healthcare professionals who manage chronic pain patients, and those in under- or postgraduate training programs, usually describe their approach to chronic pain as being based on the World Health Organization’s analgesic ladder.³ There tends to be less acknowledgment of the importance of evidence-based nonpharmacological interventions and less understanding of how to consciously include them in routine practice.

For example, existing literature on cancer pain suggests that “clinical process” (Table 1) has therapeutic value.

TABLE 1: Examples of nonpharmacological interventions used in chronic pain management

Category	Examples
Physical	Acupuncture TENS (transcutaneous electrical nerve stimulation) Healing touch and massage Occupational therapy Music and art therapy
Psychological	Hypnosis Relaxation Cognitive-behavioral therapy
Clinical process	Pain assessment Physician advice and communication about pain Education (patient, professional, family carers)

Patient satisfaction with pain management is significantly associated with a physician stating the importance of pain management, and with receiving instructions for managing pain at home, managing side effects, and allaying fears about addiction.^{4,5} Presenting an assessment of pain to physicians prior to consultation, which is then used within discussions, significantly improves pain outcomes⁶ and quality of life for patients.⁷ Use of specific prescribing guidelines for cancer pain results in significant benefit in pain intensity compared to control groups.^{8,9} Overcoming physician barriers is important,¹⁰ and these barriers relate not only to technical aspects (inadequate prescription) but also to context of the interaction with patients.¹¹ It seems likely (although specific evidence is needed) that many such simple interventions could benefit all types of chronic pains.

MECHANISMS OF ACTION

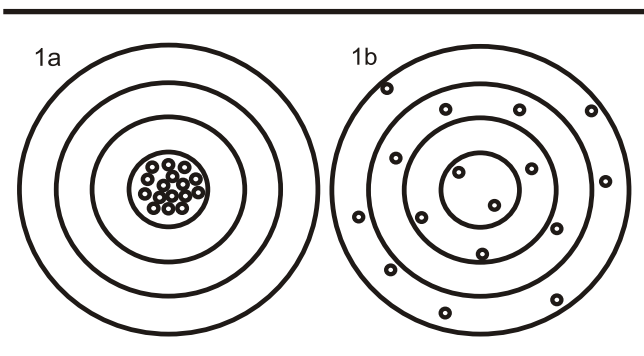
PHARMACOLOGICAL VERSUS NONPHARMACOLOGICAL INTERVENTIONS

Drug-based or pharmacological interventions usually have a precise and well-defined mechanism of action that is derived from a detailed knowledge of a particular pathophysiological mechanism involved in pain transmission and drug pharmacology. In other words, the drug is designed to intervene at a specific point in this mechanism. Examples include inhibiting an enzyme or acting as an agonist or antagonist at a specific receptor site. In clinical trials, drug-based interventions are usually given in a continuous application over several days or weeks. This approach is analogous to a rifle continuously firing precisely aimed bullets at a clear target, as shown in Fig. 1a.

In contrast, nonpharmacological interventions differ in two important respects. First, the mechanism of action is not fully understood (if at all) for many of these interventions. For example, it is not established whether acupuncture or massage affect some physiological mechanism (in either the peripheral or central nervous system) or a psychological mechanism (e.g., reduced anxiety or improved coping), or maybe both.

A common feature of nonpharmacological interventions is the focus on professional or patient behaviors, and so the mechanisms of action are often imprecise, multiple, and poorly defined. Second, these types of intervention are usually delivered as single or episodic applications, perhaps in the form of a “one-off” educational session for patients or professionals, or a series of weekly massage treatments. The result is that the effect of the intervention is intermittent, and any benefits might be harder to identify.

This approach is analogous to a shotgun firing single (or sometimes episodic) pellets that disperse around the target, shown in Fig. 1b.



COMPLEX INTERVENTIONS

Nonpharmacological interventions are probably best described as “complex interventions.”¹² This term is used for interventions that contain a combination of affects (sometimes known as bundled effects), which act through known and unknown mechanisms. Complex interventions contain several interacting components, although the complexity may arise through several dimensions, such as the number of components within the experimental and control interventions, the number and difficulty of behaviors required by those delivering or receiving the intervention, the number of groups or organizational levels targeted by the intervention, and the number and variability of outcomes.

DESIGNING THE STUDY

THE INTERVENTION ARM

In a study designed to examine a drug-based intervention, we would most likely know what dose of drug was safe and in particular, the dose and method of application to ensure that the drug affected the pathophysiological mechanism that we want to target. The same is not often true in nonpharmacological interventions, however, as we cannot always determine the “effective dose” for a complex intervention. For example, we might want to evaluate the effects of a behavioral intervention that might involve an educational leaflet, a patient diary, and three face-to-face sessions with an empathetic nurse. If we can identify the exact mechanisms of action within this complex intervention that bring about behavioral change (i.e., is it the time spent with the nurse, having the leaflet, or filling in the diary?) and understand the combined effects of these mechanisms (physicals, psychological, etc.), then we can design the study optimally. With more understanding, we might emphasize the leaflet and diary components and

reduce the face-to-face sessions, or vice versa. More usually, none of these aspects is really known or understood, and so the intervention (or the most important components of the intervention) may be “underdosed.”

Another determinant of “dose” is whether the intervention is labor intensive in its application. If an intervention is therapist or operator dependent, then the availability of such therapists or their costs may limit the number of applications or number of patients in the intervention arm. For example, if an educational intervention requires a face-to-face hour long session with an experienced practitioner repeated at weekly intervals, the financial or logistic challenges could limit the target sample size.

CHOOSING THE CONTROL ARM AND BLINDING

Designing the intervention arm is not easy, but it can be more difficult to design the control arm in these types of clinical trials because it is hard to select an appropriate control when the mechanism of action of the intervention arm is poorly understood. This difficulty is probably easier to understand when we consider the purpose of the control arm. In any clinical trial of an intervention, the aim is to distinguish the effect of the intervention (the specific effect) from the effect of other factors (the context effect) that might explain the outcome. A common approach is to standardize the context effect, which is often called a placebo, rather than a comparison with usual care (a nonstandardized context effect, which is often the most poorly defined arm of a trial). In ideal circumstances, the clinical trial would demonstrate that while context effects may be associated with some improvement in outcomes (the placebo effect), the intervention is associated with significantly more improvement (the specific effect).

The separation of specific effects from context effects is much more difficult in clinical trials of nonpharmacological interventions. In the earlier example about a behavioral intervention, we assume that the effectiveness depends on the content of the educational information (the specific effect) together with the experience and skill of the person delivering the education (the context effect).¹³ But what if the specific effect is having time with an experienced practitioner, and the information provision is merely a context effect? Interventions of this type or then better described as “bundled effects,” because it may not be possible to separate out the specific effect from the context effect. Better designed trials therefore compare three arms: usual care, placebo or attention control, and intervention. This

strategy helps to identify which context effects are most important in delivering the intervention, and indeed whether the context effects are just as effective, or even more effective, than the intervention itself.

It can be difficult to effectively blind the intervention and control arms in clinical trials of nonpharmacological interventions

Given these these constraints, unless the specific effect of the intervention is understood, some control arms in trials of nonpharmacological interventions may not really standardize the context effects. For example, when simple touch (control) was compared with massage from an experienced therapist (intervention), significant improvements occurred in both arms. with no difference over time between the two.¹⁴ A usual care group was not included in this study, but we may conclude that the specific effects (i.e., the most important effects) of this intervention are probably simple touch combined with time and attention from a practitioner, and that there is no obvious additional benefit from specialized massage techniques (which was the presumed specific effect).

BLINDING

Keeping patients, investigators, and those collecting and analyzing clinical data unaware of the assigned treatment so that they will not be influenced by that knowledge is called “blinding.” The expectation of both patients and investigators can influence findings, particularly in chronic pain where there is subjectivity in symptom assessment. Blinding is important because it is used to reduce this confounding. Not surprisingly, perhaps, it can be difficult to effectively blind the intervention and control arms in clinical trials of nonpharmacological interventions. A good example is a clinical trial of transcutaneous electrical nerve stimulation (TENS), in which the control arm may consist of a device that has no electrical output.¹⁵ It may be possible to convince the patient that the absence of sensation in the control device could still mean it is an active device, but the researcher still needs to distinguish between the devices. This aspect applies to a range of interventions such as educational interventions, acupuncture, and assessment procedures. In other words, single blinding (the patient doesn't know the allocation) may be just possible, but double blinding (the patient and researcher don't know the allocation) is almost impossible to achieve in nonpharmacological interventions, and this limitation may affect the validity of the design and interpretation of the finding

Clinical outcomes such as pain intensity or pain relief are subjective

CROSSOVER AND PARALLEL DESIGNS

Clinical outcomes such as pain intensity or pain relief are subjective, and it is usually better to use a crossover design within a clinical trial (patients cross over during the trial from control to intervention, or vice versa) rather than a parallel design (patients are allocated to either intervention or control and experience only one arm of the trial). Crossover designs allow patients to act as their own controls, which can reduce placebo response rates compared with parallel designs.¹⁶ This design largely eliminates between-patient variation, and thus the validity and reliability of the trial are greater than for a parallel trial with the same number of patients. Also, for any given level of validity or power, fewer patients are required in a crossover design than in a parallel design.

There are problems with a crossover design because the trial is often longer than a similar trial with a parallel design. Increased length introduces two difficulties. First, the patient's condition or symptom may undergo natural fluctuations such that by the time of the second arm, symptoms are naturally better or worse, regardless of the arm to which they are currently allocated. This consideration can make data analysis and interpretation difficult. Second, patients with chronic pain often have other comorbidities, and their health can deteriorate without warning.

Longer trials are more vulnerable to patients dropping out or withdrawing, either because they are too ill to continue or because they get tired of trial assessments.

Further complications of crossover designs in nonpharmacological clinical trials include "order" or "carry-over" effects, in which the effects from the first study arm on the dependent variable persist into, and influence, the second arm. For example, it is difficult to reverse the effect of an educational intervention if it was delivered in the first arm, before crossing to a control arm (and therefore a parallel design would be best for testing this type of intervention). Crossover designs may also undermine blinding. Patients allocated to an active TENS device in the first arm of a trial may very well guess that the second device is inactive when they cannot detect any tingling sensation.¹⁷

OUTCOME MEASURES

Pain intensity and pain relief are important clinical outcomes in any clinical trial in patients with chronic pain. Any assessment or measurement of effectiveness must assess these intended effects. Core outcomes measures for clinical trials in chronic pain have been recommended by IMMPACT (Initiative on Methods, Measurement, and

Pain Assessment in Clinical Trials)¹⁸ and consist of (i) pain intensity, assessed by a 0-10 numerical rating scale; (ii) physical functioning, assessed by the Multidimensional Pain Inventory and Brief Pain Inventory interference scales; (iii) emotional functioning, assessed by the Beck Depression Inventory and Profile of Mood States; and (iv) participant ratings of overall improvement, assessed by the Patient Global Impression of Change scale. It is recommended that two or more different methods be used to evaluate the clinical importance of improvement or worsening for outcome measures of chronic pain clinical trials.

However, measurement of additional outcomes in nonpharmacological trials can also be useful to help explain any observed effects or identify other benefits. This is especially relevant when the mechanism of action of the intervention is less clearly defined. Such outcomes might include coping ability, anxiety, carer distress, or medication adherence.

Choosing who measures the outcomes is equally critical. Although blinding of the allocated intervention might be difficult (for both therapist and patient), it is possible to use a blind assessor. It is clearly biased for the person applying the intervention (but not the control) to also assess the outcomes in a controlled trial, but it happens.¹⁴

Finally, timing of outcome measurement needs to be considered. Because of the intermittent or sometimes only single application of a nonpharmacological intervention, the outcomes might need to be measured immediately (e.g., massage therapy), within days to weeks (e.g., acupuncture), or over weeks to months (e.g., educational interventions). Clearly, the timing of assessment will be determined by the number of applications and the expected duration of effect, provided the mechanism is understood.

UNDERTAKING THE STUDY

RECRUITMENT

Making clinical trials attractive to patients so that they may take part in them will improve recruitment rate. One assumption is that non pharmacological interventions are less harmful than pharmacological interventions, and therefore recruiting patients to the former would be easier. There is some support for this assumption. White et al¹⁹ surveyed palliative care professional staff about referring patients to randomized controlled trials of various interventions. They found that the majority of staff would refer patients to nonpharmacological studies but were less willing to refer to pharmacological trials because of

possible adverse effects from the intervention.

In contrast, other authors have found that patients may view some nonpharmacological interventions with scepticism or lack of interest and so decline to take part in trials.²⁰ This research highlights the importance of addressing the credibility of non pharmacological interventions, as some patients with chronic pain will consider drug treatment more orthodox.

FIDELITY

In pharmacological trials, determining whether all patients received the right dose of drug for the specified duration is important in order to ensure that the drug had a chance to work. This aspect of the clinical trial is called treatment fidelity and refers to the degree to which the trial protocol was administered as intended. Treatment fidelity is probably more important in nonpharmacological trials because of the complex nature of the interventions and the potential for bias in the design.

Using a trial of TENS as an example, we need to ask if an experienced practitioner or therapist delivered the intervention but a less skilled nurse delivered the control arm. Even if a blind assessor was used, did patients reveal to them the fact that they experienced tingling feelings during the first application of TENS but not the second, and so reveal the allocation? Better quality trials report aspects of fidelity such as time spent by the therapist in each arm and asking patients whether they thought they received a placebo, and if so, in the case of crossover designs, which arm they believed to be the placebo.⁵

INTERPRETING THE DATA

Effect sizes in nonpharmacological trials are often modest, and so large sample sizes are needed to demonstrate these effects with any reliability. If the sample size is limited by constraints (discussed under “The Intervention Arm” above), then there is a high chance that any trial may be underpowered. This situation is particularly likely when no data exist on which to base a power calculation prior to undertaking the trial (which signifies that more feasibility work should have been undertaken).

Placebo responses in clinical trials for pain can be high, and the expectation of a positive effect might be greater in non pharmacological studies

Placebo responses in clinical trials for pain can be high, and the expectation of a positive effect might be considered to be greater in nonpharmacological studies. In other words, there is a greater context effect or more placebo response. Studies that tested acupuncture for chronic low back pain

showed that patient expectations of a positive result are significantly related to the actual outcomes of a positive result are significantly do less well).^{21,22} However, an analysis of pharmacological and non pharmacological interventions in the treatment of major depression suggests that the placebo response is large in both types of intervention, with no significant difference between them.²³ It is not clear whether the same holds true in trials for chronic pain.

SUGGESTIONS FOR FUTURE TRIAL DESIGN

THE ROLE OF PROCESS EVALUTION

The Medical Research Council framework for trials of complex interventions presents a phased process of trial development, moving from theory through to a definitive randomized controlled trial. This framework will allow for complex nonpharmacological interventions for pain to be investigated more effectively through the use of process evaluation before (within a feasibility study) and / or alongside an exploratory trial. It has been argued that process evaluation can explore the participants' views of the intervention, the implementation of the intervention and the influence of context on the intervention ; distinguish between components of the intervention; and describe the dose and reach of an intervention.²⁴ Qualitative investigation, often nested into trials, is becoming increasingly common as a method of process evaluation, but quantitative methods may also be used.

FEASIBILITY STUDIES

Feasibility or pilot studies test trial methodology and are not designed to formally assess the effectiveness of the intervention. In trials of nonpharmacological interventions, understanding the mechanism of action (as far as possible) and the context in which it is to operate are important before a formal evaluation is attempted. Feasibility studies can help by revealing whether the intervention is acceptable both to those providing it and those receiving it, where and by whom it should be delivered, whether it is possible to blind the intervention, what outcome measures are most appropriate, and whether changes occur in the intended domains. For example, is pain intensity reduced, or does coping improve and anxiety lesson instead? These studies can reveal insights that will then inform the design of an exploratory trial. This process is often called “modeling the intervention.”

PROCESS EVALUATIONS WITHIN TRIALS

Exploratory trials are “dress rehearsals” for definitive

randomized controlled trials. The content and delivery of a reliable, nonpharmacological intervention for chronic pain can be further improved on the basis of qualitative interviews or focus groups with patients and professionals undertaken either alongside or as part of the trial. These interviews may be done to explore patients' views of the best time and place to provide an educational intervention or a clinical guideline, and in what form. This information may help to confirm the acceptability (or not) of a given intervention and identify additional benefits perceived by participants. Process evaluation may reveal unexpected issues related to the context of the intervention, such as influences from family members ("I don't want my wife being bothered with all this—I'll read it for her," for example), which confound the anticipated outcomes. It may also generate hypotheses on the mechanism of action of the interventions.

Data from a process evaluation can add extensively to the interpretation of trial outcomes. A trial of a pain algorithm introduced into nursing practice that produced no change in pain scores might have been considered a failure.²⁵ However, consideration of the accompanying process data showed inconsistencies in the motivation and attitudes of staff, a lack of confidence in using research-based evidence, variable organizational support, a resistant ward culture, and a reliance on junior staff who were not always able to facilitate practice change. Clearly there were many factors that could not be controlled for within a complex trial of this kind, and they would have been missed unless process data had been collected.

Data from a process evaluation can add extensively to the interpretation of trial outcomes

SUMMARY

Nonpharmacological interventions are best regarded as complex interventions, and it is important to understand their mechanism of action more fully and test study methodology before formal evaluation. These aspects can be achieved through process evaluations, both by undertaking feasibility studies and monitoring trial processes along with outcomes, particularly through the use of qualitative interviews.

Many of these interventions can, and often do, help, particularly as a supplement to pharmacological intervention, but they need rigorous evaluation in order to show how to implement them in routine practice. The integration of qualitative data with trial data is not straightforward and is undergoing methodological development. Nevertheless, early work is promising, and it

is likely that this approach will be refined and used more widely in the near future.⁶

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