IASP 2023
GLOBAL YEAR
Integrative Pain Care

FACT SHEET

Generation and Appraisal of Evidence for Integrative Approaches to Pain Management

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Opportunities and Challenges

Integrative approaches to pain management include multiple treatments, often from different areas of complementary/alternative medicine, traditional medicine, or both. Individual treatments could be pain self-management, psychosocial, physical (including manual), and traditional therapies (e.g., meditation, yoga, acupuncture, ayurveda), often in combination with mainstream medical approaches such as pain medication [12]. Despite widespread use, there is limited high-quality evidence for the efficacy of many individual non-drug, and some drug interventions. Mechanisms of action are also often unclear. Combinations of interventions, as in integrative models of care, are even less well studied.

Research on non-pharmacological interventions presents unique challenges. As for pharmacological studies, the research gold-standard is the double-blind randomized controlled trial. Such blinded designs are difficult when complex interventions involve sustained interactions with providers, and they do not address real-world clinical effectiveness or interactions within integrative care. Studying integrative pain care thus requires use of different research methods than those used to study pharmacological interventions to answer pertinent questions. Here, we review factors to consider when designing and appraising research studies and highlight their roles in building the evidence base for integrative approaches to pain management[10,1].

Understanding Internal and External Validity

Internal validity is about how much confidence we can have that the studied intervention is responsible for observed changes in the results of a research study, and not confounding factor(s). Confounding variables could be personal beliefs of the experimenter and selection of participants who may respond optimally to treatment, the passage of time, or natural changes in patients' symptoms. Many research methods aim to limit such biases and thus increase internal validity. For example, randomizing patients to different groups (e.g., the experimental treatment and a control) can balance some confounding variables.

External validity is about the ability to generalize study findings to populations, settings, and contexts that are not directly studied in the trial. RCTs are often conducted in laboratory-type settings (e.g., a well-equipped university hospital) and reduce

bias by strictly limiting which patients get enrolled and how they are treated. Thus, generalizing findings of such studies to real-world contexts can be problematic. Pragmatic trials attempt to replicate 'real' clinical practice and are more likely to be generalizable but can have lower internal validity. Replicating studies in different populations, settings, and circumstances is therefore important but often not done[11].

When deciding which interventions to incorporate into integrative pain care, supportive evidence from different types of studies is required: There should be trials that focus on producing reliable trial results (i.e., have high internal validity), as well as studies that enable the implementation into a given clinical setting (i.e., have high external validity).

End-User Perspectives

Many therapies that form part of the integrative pain care are person-centered, address biopsychosocial factors, and involve communication and education to promote self-management[9]. The views and experiences of people living with pain are crucial to inform research agendas and clinical decision-making. As such, involvement of patient stakeholders in research is becoming increasingly common and is to be welcomed[8]. Specific research endeavors can increase our understanding of patient experiences by including pre- and post-study focus groups, interviews, and surveys. While qualitative methods are not discussed in detail here, all clinical research designs benefit from input from patients.

Randomized Controlled Trials (RCTs)

In drug trials, 'dummy' pills are given to one group of patients to balance the expectation of treatment benefit between study groups. Such placebo pills look the same as the pills containing the real drug and are used to 'blind' trial participants to whether they are in the treatment or the control group. Since patient expectation to get better can affect treatment outcomes, this design can distinguish between the specific effects of a drug from the beneficial effects of patient expectations. This highly controlled design also ensures that interactions with doctors and other personnel are the same in all study groups. In contrast, nonpharmacological treatments are complex and contain many more elements than pharmacological treatments that could affect patient outcomes, including more personal interactions with providers. Applying the basic idea of the placebo drug trial design to some interventions can thus be challenging. An active ultrasound device could be compared to 'treatment' with a switched-off ultrasound device, but such a 'sham' control treatment will be more difficult to design and interpret for an exercise or psychological intervention[5,6]. Albeit controversial, it is often considered important to understand whether interventions provide benefit beyond the placebo effect before integrating individual interventions into larger packages of care (as done in integrative pain care), and several commonly used interventions have limited evidence in this regard[16].

Other research methods can then be used to evaluate if treatments work in the real clinical world, or how effective combined treatments packages are. An example for such methods is the so-called 'pragmatic' trial. These are trials that more closely replicate or are embedded within real-world practice (for example, there may be more flexibility in how treatments are delivered). Pragmatic trials thus facilitate decision-making in clinics or make treatments accessible to broader populations[12]. Pragmatic trials are also often 'comparative effectiveness' trials, comparing a test intervention not against placebo but against doing nothing, receiving usual care or another established treatment[7], which are often relevant questions for integrative pain care. More creative trial designs can help understand personalized care pathways or combinations of interventions[3], as seen in integrative pain care.

Single-Case Experimental Designs (SCEDs)

SCEDs (a type of single subject or 'N-of-1' design) aim to test the effect of an intervention using a patient as their own control[15]. SCEDs prospectively collect data from an individual by repeatedly and systematically measuring outcomes (e.g., patient-reported outcomes) under two or more conditions. The systematic and frequent measurement provides scientific rigor. By sequentially applying and/or withdrawing the intervention/s in a single participant, conclusions can be drawn that are specific to that participant. Using a series of SCEDs with the same protocol allows for pooling data across participants. SCEDs are receiving more attention as interest in person-centered care is growing[14].

Strengths of SCEDs include enabling high quality research with a small number of participants, inclusion of heterogeneous participants who are often excluded from RCTs and exploration of clinical problems where the optimal interventions are uncertain or when significant individual differences in response are expected. Since no matched control group is required, this approach removes the ethical dilemma of withholding interventions from patients (as in placebo trials). SCEDs are well-suited to clinical settings and may allow clini-

cians to provide more personalized care. Limitations of SCEDs include difficulties identifying appropriate and valid outcome measures for frequent administration, participant burden due to the high number of repeated measures required to sufficiently power the study, and limited generalizability to populations outside of the study, although this can be mitigated by replication using a series of SCEDs[13,15].

Preclinical Studies

The real-world relevance of basic research with animal models or healthy human subjects is much debated. While neither fully reproduce the complexity of human chronic pain conditions, they can provide supporting evidence for efficacy, reveal underlying mechanisms, and support therapeutic optimization. The use of clinically relevant models that reflect the natural disease course in humans should be prioritized.

Basic research studies in animals and other model systems can provide evidence of efficacy in the absence of confounding placebo effects. In addition, the use of cellular model systems allows for the study of molecular and cellular effects that may not be possible in humans, such as the effect of treatments on cells in the central nervous system.

Traditional western science focuses on biological processes. While exploration of complex nonpharmacological interventions such as meditation may be difficult in preclinical models, we can explore the mechanisms underlying learning and cognitive appraisal, the impact of stress, and the importance of social interactions, for example, on the pain experience using pre-clinical models or human volunteers. Furthermore, interventions including acupuncture, stretching and massage can be studied in animals[4,2]. While understanding mechanisms is not a prerequisite for clinical use, therapeutic approaches that are grounded in known mechanisms or associated with biological changes may be more likely to be accepted by patients, health care providers, and insurers.

Finally, preclinical studies examining the transport, metabolism, and bioavailability of natural products, for example, can guide optimal use in humans, and toxicity studies can contribute to safety guidelines. Pre-clinical models can also be used to explore interactions between integrative treatments that may produce synergistic effects when used together clinically, however preclinical studies have almost exclusively studied treatments in isolation.

Conclusion

Different research methods or a combination thereof contribute to building a multifaceted evidence base for integrative pain management, informed by and centered around people with pain. Internal validity needs to be considered when drawing conclusions regarding intervention effects. At the same time, it is important to consider if study-specific conditions might impact the generalizability of the intervention results. Complicating the consideration of nonpharmacological interventions for clinical recommendations, meta-analyses and systematic reviews often discount or undervalue studies that are not double-blind RCTs or disregard necessary differences to drug trials. Increasingly, patient values and perspectives guide clinical research, and these are important factors in deciding on components of personalized integrative pain care. Overall, when designing studies or appraising existing evidence for integrative approaches to pain management, important considerations include internal and external validity, evidence from basic science, and the strengths and limitations of different study designs.

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