Evidence-based interventions to treat chronic low back pain: treatment selection for a personalized medicine approach

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Abstract
Introduction: Chronic low back pain (cLBP) is highly prevalent in the United States and globally, resulting in functional impairment and lowered quality of life. While many treatments are available for cLBP, clinicians have little information about which specific treatment(s) will work best for individual patients or subgroups of patients. The Back Pain Research Consortium, part of the National Institutes of Health Helping to End Addiction Long-termSM (HEAL) Initiative, will conduct a collaborative clinical trial, which seeks to develop a personalized medicine algorithm to optimize patient and provider treatment selection for patients with cLBP.

Objective: The primary objective of this article is to provide an update on evidence-based cLBP interventions and describe the process of reviewing and selecting interventions for inclusion in the clinical trial.

Methods: A working group of cLBP experts reviewed and selected interventions for inclusion in the clinical trial. The primary evaluation measures were strength of evidence and magnitude of treatment effect. When available in the literature, duration of effect, onset time, carryover effect, multimodal efficacy, responder subgroups, and evidence for the mechanism of treatment effect or biomarkers were considered.

Conclusion: The working group selected 4 leading, evidence-based treatments for cLBP to be tested in the clinical trial and for use in routine clinical treatment. These treatments include (1) duloxetine, (2) acceptance and commitment therapy, (3) a classification-based exercise and manual therapy intervention, and (4) a self-management approach. These interventions each had a moderate to high level of evidence to support a therapeutic effect and were from different therapeutic classes.

Keywords: Chronic low back pain, Interventions, Pragmatic clinical trial

1. Introduction

Chronic low back pain (cLBP) is common and can result in significant functional impairment and poor quality of life. Globally, cLBP affects more than one-fifth of adults in Western countries, affects female subjects more than male subjects, and is most common among individuals aged 40 to 80 years.35 Chronic low back pain is a leading cause of disability,52 and the total costs associated with cLBP exceed 100 billion dollars per year in the United States alone,23,40 with the great majority related to loss in wages and productivity.

The most commonly used treatments for cLBP are exercise, manual therapy, psychological therapies, such as cognitive behavioral therapy (CBT), medication management, targeted interventional procedures, education, and self-management.9,47,48,54,58 With similarly small- to moderate-sized treatment effects for many of these therapies and large variability in individual responses, it is likely that there are subgroups with enhanced treatment effects. And yet there are currently no proven approaches to identify these subgroups in daily clinical practice. Furthermore, there are no clear...
Key Points

1. A range of treatments for chronic low back pain (cLBP) exist but most have small to moderate-sized treatment effects and vary widely in individual responses. It is likely that there are subgroups with enhanced treatment effects but there are currently no proven approaches to identify these subgroups in daily clinical practice. The Back Pain Research Consortium (BACPAC) reviewed evidence-based interventions to select interventions for use in a collaborative, precision medicine study to find the best treatment based on an individuals’ phenotype.

2. There is moderate evidence that exercise, regardless of type, offers a moderate clinical benefit. The effect of exercise is strengthened when a protocolized, classification-based approach based on patient presentation is used.

3. Effective behavioral treatments include cognitive behavioral therapy, mindfulness-based treatments, and acceptance and commitment therapy. Acceptance and commitment therapy incorporates components of mindfulness and increases psychological flexibility in patients with pain.

4. There is moderate evidence that both guided and unguided self-management programs have a moderate effect size. An unguided self-management program is cost-effective and scalable.

5. There is a high level of evidence that the use of SNRI such as Duloxetine for patients with cLBP has a moderate treatment effect.

2. Methods

2.1. Description of expert panel

In the second year of BACPAC, an IWG was convened and charged with selecting interventions for inclusion in a collaborative clinical study (CCS). Composed of researchers and practitioners with expertise in low back pain and training in physical therapy, chiropractic, psychology, psychiatry, pain management, and/or orthopedic research, the IWG evaluated the available literature to identify the leading evidence-based interventions.

2.2. Framework for evaluating and selecting interventions

The IWG established a framework for evaluating the merits of interventions for inclusion in the CCS and is shown in Table 1. IWG members established a comprehensive list of candidate interventions, which is shown in Table 2. The working group ranked the strength of evidence and magnitude of treatment effect based on guidelines in the Global Spine Journal. The group sought to include interventions that have a high level of evidence (based on strength of evidence and magnitude of treatment effect) and would be practical to administer in a clinical study (and in a real-world clinical setting) to a wide range of patients suffering from cLBP.

When available, duration of effect, onset time, and carryover time were also considered in the decision-making process. Additionally, when available, interventions were evaluated for multimodal efficacy, evidence for the mechanism of treatment effect or biomarkers, and evidence of responder subgroups. Drawing upon clinical literature as well as upon clinical pragmatism, the expert panel also evaluated barriers to adherence, fidelity, and implementation. These criteria were relevant to the intervention selection for the trial as well as to clinical practice.

Using this framework, IWG members reviewed selected interventions from 7 categories: movement therapy, behavioral treatments, self-management, manual therapies, acupuncture, medications, injections, multidisciplinary rehab, and innovative treatments (See Table 2 for full list of candidate interventions). Members were assigned to assess interventions based on their clinical and research expertise and then compiled the findings in a spreadsheet and reports to the larger working group. The goal of this process was to select the 4 leading interventions to be included in a precision medicine trial based on best available...
Interventions reviewed by the IWG are summarized below.

3. Results

The evidence for each intervention category is described below.

3.1. Movement therapy

Four types of movement therapy were reviewed: (1) walking programs, (2) general exercise, which typically combines strength training and conditioning, (3) motor control exercise, and (4) directional preference exercise. Across the board, there was moderate strength of evidence and moderate effect sizes for most types of exercise, although no specific exercise modality outperformed others.6,11,18,29,37,51,52,55,56,61 The effect size of exercise improved when combined with CBT, 29 manual therapy, 61 or decision-making strategies to tailor treatment to individual patients (eg, implementing a decision tree to help providers choose the best exercise for patients).6,55 Mind–body interventions, such as Qigong or yoga involving movement, were not reviewed by the working group; these exercises, like other exercise modalities, have a moderate effect, but present scaling challenges for widespread clinical implementation.53,56 After weighing the array of movement therapies to address cLBP, the working group recommended a protocolized classification-based approach that is led by physical therapists or chiropractors and incorporated decision making based on patient presentation, rather than a specific type of exercise. This is an approach that may improve overall effects of exercise on cLBP. 6,19,30,33 The moderate clinical evidence 19,30,33 indicated that this approach would, for example, use extension based exercises to treat patients who experience a preference for standing vs sitting.38 The literature supported that such a classification-based approach to physical therapy may result in large effects on pain intensity and disability. The classification-based approach also typically integrated manual therapy and cognitive-behavioral principles, which also may result in larger treatment effects. 29,61

| Table 2 |
| Evidence table for interventions examined. |
| Intervention | Category | Strength of evidence (SOE) (high, moderate, low, insufficient) | Magnitude of treatment effect (MOT) (small, moderate, large) |
| Interventions selected | | | |
| Acceptance and commitment therapy (ACT) | Behavioral | High | Small |
| Antidepressants: SNRI Medication | Medication | High | Moderate |
| Classification-based exercise management (ie, matching exercise to individual physical and psychological factors) | Movement | Moderate | Large |
| Behavioral self-management (education) | Self-management | Moderate | Moderate |
| Acceptance and commitment therapy (ACT) | Behavioral | High | Small |
| Antidepressants: SNRI Medication | Medication | Moderate | Moderate |
| Antidepressants: SSRI/TCA Medication | Medication | Moderate | Small |
| Muscle relaxants | Medication | Moderate | Small |
| Walking program | Movement | Moderate | Moderate |
| General exercise programs | Movement | Moderate | Moderate |
| Motor control exercise (MCE) | Movement | Moderate | Moderate |
| Decisional preference exercise (McKenzie) | Movement | Moderate | Moderate |
| Exosuit/robotic apparel | Novel intervention/Device | Low | Moderate |
| Multidisciplinary rehabilitation | Rehabilitation | Moderate | Moderate |
| Digital behavioral self-management (self-guided) | Self-management | Moderate | Moderate |
| Acupuncture self-management | Surgery | Low | Moderate |
| Basivertebral nerve ablation | | | |
| NSAIDs | | | |
| Anticonvulsants | | | |
| Antidepressants: SSRI/TCA | | | |
| Muscle relaxants | | | |
| Walking program | | | |
| General exercise programs | | | |
| Motor control exercise (MCE) | | | |
| Decisional preference exercise (McKenzie) | | | |
| Exosuit/robotic apparel | | | |
| Multidisciplinary rehabilitation | | | |
| Digital behavioral self-management (self-guided) | | | |
| Acupuncture self-management | | | |
| Basivertebral nerve ablation | | | |
| Acupuncture | | | |
| Mindfulness-based stress reduction (MBSR) | Behavioral | Moderate | Moderate |
| Mindfulness-based cognitive therapy (MBCT) | Behavioral | Low | Moderate |
| Cognitive skills-based virtual reality therapy | Behavioral | Moderate | Moderate |
| Cognitive behavioral therapy (CBT) | Behavioral | Moderate | Moderate |
| Education | Behavioral | Variable | Variable |
| Acupuncture: Practitioner provided | Complementary medicine | Low to moderate | Moderate |
| Epidural steroid injections | Injections | Moderate | Moderate |
| Lumbar facet radiofrequency lesioning | Injections | Moderate | Moderate |
| Massage | Manual therapy | Low | Small |
| Spinal manipulation | Manual therapy | Low to moderate | Moderate |
| NSAIDs | Medication | Low to moderate | Moderate |
| Anticonvulsants | Medication | Low | Small |
| Antidepressants: SSRI/TCA | Medication | Moderate | Moderate |
| Muscle relaxants | Medication | Low | Moderate |
| Walking program | Movement | Moderate | Moderate |
| General exercise programs | Movement | Moderate | Moderate |
| Motor control exercise (MCE) | Movement | Moderate | Moderate |
| Directional preference exercise (McKenzie) | Movement | Moderate | Moderate |
| Exosuit/robotic apparel | Novel intervention/Device | Low | Moderate |
| Multidisciplinary rehabilitation | Rehabilitation | Moderate | Moderate |
| Digital behavioral self-management (self-guided) | Self-management | Moderate | Moderate |
| Acupuncture self-management | Self-management | Low | Moderate |
| Basivertebral nerve ablation | Surgery | Moderate | Moderate |

NSAID, nonsteroidal anti-inflammatory drug.
3.2. Behavioral Treatments

Interventions working group members reviewed cognitive behavioral therapy (CBT), acceptance and commitment therapy (ACT), mindfulness-based therapies, and cognitive skills-based virtual reality (VR). While biofeedback and specific diets (eg, anti-inflammatory) were initially considered as potential behavioral treatments, the evidence for both interventions was weak, and they were therefore removed from further consideration.

Cognitive behavioral therapy is well-studied with reliable small-to-medium effects on disability and pain catastrophizing for patients with cLBP. Cognitive behavioral therapy is often multimodal, with CBT approaches regularly deployed in combination with other therapies. Cognitive behavioral therapy has a quick onset, and its effects may persist for 6 to 12 months. Individuals with higher negative affect and greater distress at baseline tend to respond more favorably to CBT. Acceptance and commitment therapy has high strength of evidence with an effect size similar to CBT. Evidence from chronic pain trials, which typically include cLBP patients, demonstrated a moderate treatment effect size. A high-responding phenotype was not identified in the literature. Delivered by licensed mental health providers, ACT was specifically developed to improve function and pain via teaching behavioral approaches that lead to acceptance of the pain vs gaining control over the pain.36,62

Although VR therapies showed promise, only one pilot randomized control trial of VR in low back pain had been completed at the time of intervention selection, in which pain intensity and pain interference improved among those receiving skills-based VR.12 One additional randomized trial had been completed since that time in which clinically meaningful reductions in average pain intensity and pain interference improved compared with a placebo VR group were found.27 While a self-administered, app-based VR program may reduce barriers to traditional in-person behavioral therapies, there was insufficient evidence of its efficacy at the time of intervention selection. There could also be implementation barriers when recruiting from clinical settings as the published studies recruited from a convenience sample on social media platforms who might have higher confidence in use of technology. The mindfulness interventions we considered included both mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT). The strength of evidence for MBSR was moderate, and the effect size was small to medium, with an unclear duration of effect. While one meta-analysis showed only a short-term effect on pain intensity and function, other data are indicative of a robust long-term effect on pain severity and interference.3,7,58 MBSR is a protocol-driven intervention that requires a trained facilitator but not a licensed professional. However, the time commitment (usually 26 hours in classes plus 30 minutes daily home practice over 8 weeks) may be burdensome to patients and providers. This limitation contributed to the exclusion of MBSR from this study. Studies showed that patients with lower scores on mindfulness inventories benefited most from MBSR and patients with lower baseline levels of pain catastrophizing responded best to MBCT.13 The strength of evidence for MBCT as a treatment for low back pain was low, due to limited studies of the intervention, and was therefore not selected for this study. Furthermore, the delivery of MBCT requires extensive provider training. Based on the strength of evidence, the working group recommended that ACT, which includes several key elements of mindfulness techniques, be included as an intervention for the CCS. Acceptance and commitment therapy was chosen over CBT because of the strength of evidence for cLBP and evidence that it is perhaps more effective in subgroups of patients, such as in those with lower education levels and/or advanced age.

3.3. Self-management

Acupuncture, in-person self-management, and digital self-management were also reviewed. There was low-to-moderate strength of evidence for provider-led acupuncture. A 6-study meta-analysis found a 50% decrease in pain intensity for treatment groups, although the effect on disability was not significant.28 However, significant barriers in terms of provider time and insurance coverage limit its use in a pragmatic clinical trial. Acupuncture can also be used as a self-management strategy with an at-home device. Although there was evidence of moderate effect on disability and fatigue, the strength of evidence was low as self-guided acupuncture has not been well-studied in low back pain, which is why this intervention was not selected for the collaborative trial.48 While the technique can be easily taught and implemented, it requires a high level of patient engagement.

Pain self-management programs encompass a range of skills and techniques that can be learned and practiced by the patient independently. The teaching of the skills is often facilitated by a licensed professional, but it can be taught by lay leaders or peer advocates. The treatment effect size of self-management on pain intensity in the short term was moderate (eg, 0.29) and appears capable of retaining its benefits over longer-term follow-up (eg, 0.25). Self-management programs also supported improvement in other outcomes, such as pain beliefs and self-efficacy and functional status.16 Individuals with hypersensory sensitivity and both hypersensory sensitivity and psychosocial challenges tended to respond best to both guided and self-guided pain management programs.16 Because of these well-studied positive attributes, pain self-management was chosen as an intervention for the collaborative study.

Some self-management programs are entirely self-guided without a therapist. They often include scientific information regarding chronic pain, instructions on how to use various self-management skills, and homework assignments that also help to monitor progress. An analysis of these unguided programs reported effect sizes similar to that of guided, face-to-face programs on pain intensity. Like guided programs, the treatment effect was strongest immediately after intervention and at short-term follow-up but benefits diminish only slightly over time.18 Some studies found that a therapist or coach provided a slightly stronger effect and may have buffered against the slightly higher attrition rate found in the unguided format.59 Nevertheless, an unguided digital self-management program is highly cost-effective and is easily scaled for clinical implemented across study sites. The panel recommended digital self-management as a standalone intervention or as a first-line treatment in the CCS.

3.4. Manual Therapies/acupuncture

Massage, acupuncture, and spinal manipulation were also reviewed. Massage had a moderate effect for pain (standardized mean difference −0.75, 95% confidence interval [CI] −0.90 to −0.60)24 and had a small to moderate effect on function, with estimated reduction in pain ranging from −0.38 (95% CI −0.63 to −0.20)58 to −0.72 (95% CI −1.05 to −0.39);24 Although onset of improvement may be immediate, the duration of effect was limited, requiring repeated massages. The overall strength of evidence for massage was low, leading to exclusion from the study.24

The strength of evidence for acupuncture was low to moderate and literature on its effect is mixed. Studies have found a small or
medium effect on pain; reviews report $-0.54$ decrease on a 0 to 10 scale (95% CI $-0.91$ to $-0.16$)
$^{25}$ or $-0.75$ decrease (95% CI $-0.94$ to $-0.49$).\textsuperscript{8} respectively. On function, reviews indicate no effect, a small effect (SMD $-0.23$, 95% CI $-0.35$ to $-0.04$),\textsuperscript{58} or large effect (SMD $-0.94$ [95% CI $-1.41$ to $-0.47$])\textsuperscript{58} compared with inactive control for function. The benefits of acupuncture may persist up to 6 months.\textsuperscript{58} Spinal manipulation’s evidence was low to moderate and literature found a small effect on function (SMD $-0.34$, 95% CI $-0.75$ to $-0.02$) and minimal-to-
low effect on pain ($-0.64$, 95% CI $-0.93$ to $-0.35$).\textsuperscript{58} Literature suggested that patients with acute pain responded more to spinal manipulation than those with chronic low back pain.\textsuperscript{58} Massage, acupuncture, and manipulation each require repeated sessions and may be delivered with a wide variety of techniques, which may be barriers to widespread implementation and fidelity across sites in the collaborative trial.

### 3.5. Injections

There was moderate evidence that both epidural steroid and lumbar facet injections offer moderate effects on pain. With an onset time of 1 to 2 weeks, injections may provide improvement in an intermediate time frame. Evidence suggested that injections may have a stronger effect on specific subgroups, particularly patients with radicular pain.\textsuperscript{22,57,60} It is because of this fact that the panel did not recommend injections as a treatment in the collaborative study, although injections may be effective for managing low back pain in subgroups of patients.

### 3.6. Multidisciplinary rehabilitation

Moderate evidence supported a small treatment effect for multidisciplinary rehabilitation.\textsuperscript{8,9} Multidisciplinary rehabilitation involves addressing pain using a team approach with providers from different disciplines providing treatment of the physical, social, and psychological impacts of chronic pain.\textsuperscript{39,45} Multidis-

ciplinary rehabilitation presents unique challenges for a multisite trial or in typical community practice: interventions tend to be more complex and require a high level of care coordination among a team (eg, team meetings to review patient progress), making execution across multiple sites or in community practices more difficult without the proper infrastructure and training. While there is no clear phenotype for a positive treatment response, patients with higher disability, higher functional impairment, and psychosocial problems tended to respond better to multidisci-


ciplinary approaches.\textsuperscript{8,9} Because of the complexity of delivering a complex team-based intervention across many sites, multidisci-


phinary nerve ablation (BNA) is another promising intervention with moderate evidence of short-term and long-
term treatment effect (20.9 reduction in ODI at 3 months; 25.95 reduction in ODI at 5 years).\textsuperscript{41} Basivertebral nerve ablation is a minimally invasive procedure indicated in patients suffering from cLBP with a diagnosis of type 1 or type 2 Modic change on magnetic resonance imaging.\textsuperscript{20,21} This procedure involves the use of radiofrequency ablation technology to destroy the basivertebral nerve, which provides sensory innervation to the endplates. Based on the available evidence, basivertebral nerve ablation is a potentially promising second-line intervention for nonresponders to first-line, conservative management of cLBP.

### 3.7. Medications

Several classes of nonopioid medications were reviewed: anticonvulsant drugs, muscle relaxants, nonsteroidal anti-


inflammatory drug (NSAIDs), SSRI/TCA, and SNRIs.\textsuperscript{54} The strength of evidence for prolonged used of muscle relaxants was low, and studies did not support a treatment effect; similarly, most studies of SSRI/TCA did not identify a treatment effect either.\textsuperscript{54} Anticonvulsants (eg, gabapentin) had low evidence of small-to-moderate effect, and the best evidence of treatment effect was in patients who have radicular pain. Nevertheless, anticonvulsants are widely used in practice. Well-studied in efficacy trials and widely used, NSAIDs have been shown to offer a moderate treatment effect.\textsuperscript{54}

SNRIs are also commonly prescribed to treat cLBP. Compared with other antidepressants (eg, SSRI, TCA), SNRIs performed best in trials and had a high-level evidence of moderate treatment effect.\textsuperscript{1,34} The effect of SNRI on cLBP may persist longer than other medications.\textsuperscript{37,54} Duloxetine, an SNRI, is in current use as an intervention in 2 BACPAC studies, and there are few identifiable barriers to adherence or fidelity. Therefore, based on the strength of evidence for a moderate treatment effect, duloxetine was recommended for inclusion as an intervention for the CCS. Use of NSAIDs was incorporated into the self-


management arm discussed above because they are commonly used in their over-the-counter formulation.

### 3.8. Innovative/emerging treatments

Novel procedures and assistive devices may mitigate low back pain, though evidence for emerging treatments was limited. The panel reviewed body-worn assistive technologies (eg, exosuits or exoskeletons) and basivertebral nerve ablation. Initial data on exosuits were limited but promising. Reduced musculoskeletal loads were observed in healthy control, with consistent decreases in EMG amplitudes (10%–40% reduction) and back/hip extensor moments and forces (10%–30% reduction).\textsuperscript{44} Studies of exosuits in patients with LBP reported immediate psychological benefits, including feeling of support, reduced task effort, and increased task self-efficacy.\textsuperscript{4,5,42,59} However, the efficacy of these novel devices was task dependent, and the devices require further testing with symptomatic populations, validation in combination with other therapies, and guideline development.

Basivertebral nerve ablation (BNA) is another promising intervention with moderate evidence of short-term and long-
term treatment effect (20.9 reduction in ODI at 3 months; 25.95 reduction in ODI at 5 years).\textsuperscript{41} Basivertebral nerve ablation is a minimally invasive procedure indicated in patients suffering from cLBP with a diagnosis of type 1 or type 2 Modic change on magnetic resonance imaging.\textsuperscript{20,21} This procedure involves the use of radiofrequency ablation technology to destroy the basivertebral nerve, which provides sensory innervation to the endplates. Based on the available evidence, basivertebral nerve ablation is a potentially promising second-line intervention for nonresponders to first-line, conservative management of cLBP.

### 4. Conclusion

The exciting promise of the BACPAC CCS is the ability to match patient phenotype to treatment through a precision medicine approach. The study will determine the differential impact of phenotype on response to treatment. There is a diverse range of interventions with proven effectiveness that can be used in the management of cLBP in routine clinical practice. The recom-
dendations of the multidisciplinary expert panel convened for the selection of evidence-based treatments for cLBP to be tested in the collaborative clinical trial are also applicable to clinical practice for the management of patients with cLBP. This expert panel selected the following, multifaceted, evidence-based treatments for cLBP: (1) duloxetine, (2) ACT, (3) a classification-based exercise and manual therapy intervention (evidence-based exercise and manual therapy), and (4) a self-management approach (enhanced self-care). Incorporating data from extensive patient phenotyping, these therapies will be tested in the sequential, multiple-assignment, randomized collaborative trial to generate a precision medicine algorithm that will enable physicians to tailor bedside decision making for the patient experiencing cLBP. Deriving patient phenotypes that best
respond to a particular intervention will enable stratification of patients seen in clinical practice to the optimal treatment. The findings of our working group may also help the selection of treatments for chronic back pain amongst practitioners, using an evidence-informed and personalized approach.

Disclosures

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