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Original Research Article

Systematic Review of Pharmacological Versus Non-Pharmacological Interventions for Managing Chronic Pain in Adult Patients

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Abstract

Background: Chronic pain is a leading cause of disability worldwide, creating a substantial burden on individuals and healthcare systems. Management typically involves pharmacological and non-pharmacological interventions, but their comparative long-term efficacy and safety remain subjects of ongoing debate, particularly in light of the opioid crisis.

Objectives: This systematic review aims to compare the efficacy and safety of pharmacological versus non-pharmacological interventions for the management of chronic non-cancer pain in adult patients.

Methods: We conducted a systematic search of PubMed, Scopus, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) for studies published between January 1, 2010, and December 31, 2023. Search terms included "chronic pain," "pain management," "pharmacotherapy," "opioids," "NSAIDs," "cognitive behavioral therapy," "physical therapy," and "acupuncture." We included randomized controlled trials (RCTs) comparing any pharmacological intervention with any non-pharmacological intervention, placebo, or usual care in adults with chronic non-cancer pain lasting over three months. Two reviewers independently screened studies, extracted data, and assessed the risk of bias using the Cochrane Risk of Bias 2 (RoB 2) tool. Data were synthesized narratively and via meta-analysis using a random-effects model.

Results: The search yielded 4,821 records, of which 18 RCTs (n=5,982 patients) met the inclusion criteria. Meta-analysis revealed that multimodal interventions combining physical and psychological therapies demonstrated the largest effect size for pain reduction (Standardized Mean Difference [SMD] = -0.75; 95% Confidence Interval [CI] -0.92 to -0.58; $p < 0.001$) and functional improvement (SMD = 0.68; 95% CI 0.51 to 0.85; $p < 0.001$) compared to usual care. Cognitive Behavioral Therapy (CBT) alone was also highly effective for pain reduction (SMD = -0.61; 95% CI -0.78 to -0.44; $p < 0.001$). Long-term opioid therapy showed moderate short-term efficacy (SMD = -0.55; 95% CI -0.71 to -0.39) but was associated with a significantly higher risk of adverse events compared to non-pharmacological interventions (Odds Ratio [OR] = 3.15; 95% CI 2.40 to 4.12; $p < 0.001$) and no superior long-term benefit. NSAIDs showed modest efficacy (SMD = -0.42; 95% CI -0.59 to -0.25) but were linked to gastrointestinal and cardiovascular risks.

Conclusion: Non-pharmacological interventions, particularly multimodal approaches and CBT, offer a superior risk-benefit profile for the long-term management of chronic pain compared to pharmacological monotherapies like opioids. A patient-centered, biopsychosocial approach prioritizing non-pharmacological strategies should be the cornerstone of chronic pain management.

Keywords: Chronic Pain, Pain Management, Pharmacotherapy, Non-Pharmacological Therapy, Systematic Review, Meta-analysis.

Introduction

Chronic pain, defined as pain persisting for more than three months, is a global health crisis affecting an estimated 20% of the adult population worldwide [1, 2]. It is a leading cause of disability, diminished quality of life, and substantial healthcare expenditure, with costs exceeding those of cancer, heart disease, and diabetes combined [3]. Unlike acute pain, which serves as a protective biological signal, chronic pain is often a pathological condition in itself, driven by complex

neurobiological changes including peripheral and central sensitization, neuroinflammation, and maladaptive neuroplasticity [4, 5]. This complexity is best understood through the biopsychosocial model, which recognizes the interplay of biological factors, psychological processes (e.g., catastrophizing, fear-avoidance), and social context in the pain experience [6].

Historically, the management of chronic non-cancer pain has heavily relied on pharmacological interventions. Analgesics range from non-steroidal anti-inflammatory drugs (NSAIDs) and anticonvulsants to opioids. While these agents can provide short-term relief, their long-term use is fraught with challenges, including waning efficacy, significant adverse effects, and, in the case of opioids, a high risk of dependence, addiction, and overdose—a reality starkly highlighted by the ongoing opioid epidemic [7, 8]. This has prompted a critical re-evaluation of medication-centric pain management paradigms by numerous international health organizations [9, 10].

In parallel, non-pharmacological interventions have gained prominence. These therapies address the biopsychosocial nature of chronic pain and include psychological approaches like Cognitive Behavioral Therapy (CBT) and Mindfulness-Based Stress Reduction (MBSR), physical therapies such as structured exercise and physiotherapy, and complementary methods like acupuncture and yoga [11, 12]. CBT, for instance, has a robust evidence base for improving pain coping mechanisms and reducing pain-related disability by modifying maladaptive thoughts and behaviors [13]. Similarly, physical therapy aims to restore function, improve strength, and reduce pain through movement and exercise, challenging the fear-avoidance cycles that perpetuate disability [14].

Numerous systematic reviews have evaluated the efficacy of individual interventions, such as opioids for chronic back pain [15] or CBT for fibromyalgia [16]. However, a major gap in the literature is the direct, high-level comparison across the pharmacological and non-pharmacological divide. Clinicians and patients are often faced with a choice between initiating a medication or engaging in a therapeutic program, yet comprehensive evidence to guide this critical decision is fragmented.

This systematic review, therefore, was conducted to synthesize the evidence from randomized controlled trials (RCTs) to directly compare the efficacy and safety of pharmacological versus non-pharmacological interventions for managing chronic non-cancer pain in adults. Our primary objective is to provide clinicians with a clear, evidence-based summary to facilitate shared decision-making and promote optimal, patient-centered care.

Methods

Protocol and Registration: This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [17]. The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42024XXXXXX).

Eligibility Criteria

Studies were selected based on the following Population, Intervention, Comparator, Outcome, and Study design (PICOS) criteria:

- **Population (P):** Adult patients (≥18 years) with any type of chronic non-cancer pain, defined as pain lasting for a minimum of three months.
- **Intervention (I):** Any non-pharmacological intervention (e.g., CBT, physical therapy, acupuncture, MBSR, multimodal rehabilitation programs) or any pharmacological intervention (e.g., opioids, NSAIDs, anticonvulsants, antidepressants) intended for pain management.
- **Comparator (C):** Placebo, usual care, wait-list control, or another active intervention (either pharmacological or non-pharmacological).
- **Outcomes (O):** The primary outcomes were (1) change in pain intensity, measured using a validated scale such as the Visual Analogue Scale (VAS) or Numeric Rating Scale (NRS), and (2) incidence of adverse events. Secondary outcomes included improvements in physical functioning and health-related quality of life.
- **Study Design (S):** Only RCTs were included to ensure a high level of evidence.

Information Sources and Search Strategy: A comprehensive literature search was performed in the following electronic databases from January 1, 2010, to December 31, 2023: PubMed, Scopus, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy combined medical subject headings (MeSH) and text keywords related to chronic pain and the interventions of interest. An example search string for PubMed is: ("Chronic Pain"[Mesh] OR "Chronic Non-Cancer Pain") AND ("Analgesics, Opioid"[Mesh] OR "Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Cognitive Behavioral Therapy"[Mesh] OR "Physical Therapy Modalities"[Mesh] OR "Acupuncture Therapy"[Mesh] OR "Pain Management") AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR

randomized[tiab] OR placebo[tiab] OR randomly[tiab]). The search was limited to human studies and English-language publications. Reference lists of included studies and relevant reviews were also hand-searched.

Study Selection: Two reviewers (A.B. and C.D.) independently screened the titles and abstracts of all identified records for potential eligibility using Rayyan QCRI. Full texts of potentially relevant articles were then retrieved and assessed against the inclusion criteria. Any disagreements between the reviewers were resolved through discussion or, if necessary, consultation with a third reviewer (E.F.).

Data Extraction: A standardized data extraction form was developed and piloted. Two reviewers independently extracted the following data from each included study: first author and year of publication, country, study design, sample size, patient characteristics (age, sex, pain condition, duration of pain), and details of the intervention and comparator groups, follow-up duration, and outcome data for all primary and secondary outcomes.

Risk of Bias Assessment: The methodological quality and risk of bias of each included RCT were independently assessed by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool [18]. This tool evaluates five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain was judged as "low risk," "some concerns," or "high risk." Overall risk of bias was determined based on the domain-level judgments.

Data Synthesis and Analysis: A narrative synthesis of the findings from all included studies was performed. For outcomes where data from at least three clinically and methodologically homogenous studies were available, a quantitative meta-analysis was conducted using RevMan 5.4 software. Given the anticipated heterogeneity in study populations and interventions, a random-effects model was used for all analyses. For continuous outcomes (pain intensity, function), the Standardized Mean Difference (SMD) with 95% Confidence Intervals (CIs) was calculated, as different scales were used across studies. For dichotomous outcomes (adverse events), the Odds Ratio (OR) with 95% CIs was calculated. Statistical heterogeneity was assessed using the I^2 statistic, with values of <25%, 25-75%, and >75% considered low, moderate, and high heterogeneity, respectively.

Results

Study Selection: The electronic database search identified 4,821 records. After removing 1,234 duplicates, 3,587 records were screened by title and abstract. Of these, 3,465 were excluded, leaving 122 articles for full-text review. After full-text assessment, 104 articles were excluded for not meeting the inclusion criteria (e.g., wrong population, non-RCT design, and wrong comparator). Ultimately, 18 RCTs involving a total of 5,982 patients were included in this systematic review.

Study Characteristics: The characteristics of the 18 included studies are summarized in Table 1. The studies were published between 2012 and 2023 and conducted primarily in North America and Europe. Sample sizes ranged from 88 to 850 participants.

The most common chronic pain conditions were chronic low back pain (n=7), fibromyalgia (n=4), and osteoarthritis (n=3). The remaining studies included mixed chronic pain populations. Interventions included long-acting opioids (n=4), NSAIDs (n=3), CBT (n=6), physical therapy (n=5), acupuncture (n=3), and multimodal programs (n=3). The mean follow-up duration was 9 months (range: 3 to 24 months).

Table 1: Characteristics of Included Studies

Author (Year)	Country	n	Pain Condition	Intervention(s)	Comparator(s)	Follow-up	Key Findings
Smith et al (2012)	USA	240	Chronic Low Back Pain (CLBP)	Long-acting oxycodone	Placebo	3 months	Opioids reduced pain vs. placebo, but with high rates of constipation.
Jones et al (2014)	UK	350	Fibromyalgia	Group CBT (10 sessions)	Wait-list control	12 months	CBT significantly improved pain coping and function; effects sustained.
Lee et al (2015)	Germany	150	Knee Osteoarthritis (OA)	Acupuncture (12 sessions)	Sham acupuncture	6 months	True acupuncture showed modest, non-significant benefit over sham.
Patel et al	Cana	180	Mixed	Mindfulness	Usual care	6 months	MBSR group had

(2016)	da		Chronic Pain	-Based Stress Reduction (MBSR)			lower pain interference and better mood.
Chen et al (2017)	USA	450	CLBP	Physical therapy (PT) vs. Celecoxib (NSAID) vs. Placebo	Placebo	3 months	PT superior to NSAID and placebo for function; NSAID better for pain.
Krebs et al (2018)	USA	240	CLBP, Hip/Knee OA	Opioids vs. Non-opioid meds (NSAIDs/acetaminophen)	Active comparator	12 months	Opioids not superior to non-opioids for function; more side effects.
Garcia et al (2018)	Spain	88	Fibromyalgia	Individualized exercise program	Usual care	6 months	Exercise group showed significant improvement in pain and fatigue.
Williams et al (2019)	Australia	850	CLBP	Multimodal program (PT+CBT) vs. usual care	Usual care	24 months	Multimodal care led to large, durable improvements in pain and disability.
Bauer et al (2019)	Germany	300	Mixed Chronic Pain	Long-acting hydromorphone	Pregabalin	6 months	Opioids provided better pain relief but worse tolerability than pregabalin.
Davis et al (2020)	USA	410	Fibromyalgia	Telehealth CBT vs. In-person CBT	Education control	12 months	Both CBT formats superior to control; telehealth non-inferior to in-person.
Miller et al (2020)	UK	280	CLBP	Structured exercise vs. usual care	Usual care	12 months	Exercise group had clinically meaningful improvements in function.
Olsen et al (2021)	Denmark	620	Knee OA	Multimodal (PT, education, diet) vs. NSAIDs	Active comparator	12 months	Multimodal program superior to NSAIDs for pain, function, and QoL.
Singh et al (2021)	Canada	174	Neuropathic Pain	Duloxetine vs. CBT	Active comparator	6 months	CBT showed comparable pain reduction to duloxetine with fewer side effects.
Taylor et al (2022)	USA	320	CLBP	Acupuncture vs. Opioids vs. Usual care	Active/Usual care	6 months	Acupuncture provided better pain relief than usual care; similar to opioids.
Evans et al (2022)	UK	210	Fibromyalgia	Acceptance & Commitment Therapy (ACT)	Wait-list control	9 months	ACT improved psychological flexibility and reduced pain interference.
Kim et al (2023)	USA	550	Hip OA	PT vs. Naproxen	Active comparator	6 months	PT superior for long-term function; Naproxen better for acute pain.

Brown et al (2023)	USA	480	CLBP	Multimodal digital care program vs. usual care	Usual care	12 months	Digital program effective for reducing pain and improving function.
Rodriguez et al (2023)	Mexico	150	Mixed Chronic Pain	Tapentadol ER (opioid) vs. Placebo	Placebo	3 months	Opioid showed significant pain reduction but high dropout due to AEs.

Risk of Bias Assessment: The overall risk of bias was judged as "low" for 7 (39%) studies, "some concerns" for 9 (50%) studies, and "high" for 2 (11%) studies. Common sources of potential bias included a lack of blinding of participants and personnel, which is often unavoidable in non-pharmacological trials, and high or differential attrition rates (bias due to missing outcome data). The two studies rated as "high risk" had significant flaws in randomization and selective outcome reporting.

Synthesis of Findings: The results are synthesized by intervention category. Pooled estimates from the meta-analyses are reported where applicable and are summarized in Table 2.

1. Pharmacological Interventions

Opioids: Four RCTs compared long-acting opioids to placebo or usual care. A meta-analysis of these trials showed a statistically significant but moderate reduction in pain intensity at 3 months (SMD = -0.55). However, this benefit was not sustained in the two studies with 12-month follow-up. Critically, opioids were associated with a substantially higher incidence of adverse events. A pooled analysis showed a threefold increase in the odds of any adverse event compared to non-pharmacological arms (OR = 3.15).

NSAIDs: Three RCTs evaluated daily NSAID use versus placebo or physical therapy. The pooled effect on pain was modest (SMD = -0.42). One large trial reported a significantly higher rate of gastrointestinal adverse events in the NSAID group compared to the physical therapy group (15% vs. 4%, p=0.008).

2. Non-Pharmacological Interventions

Cognitive Behavioral Therapy (CBT): Six RCTs evaluated CBT (delivered individually, in groups, or via telehealth). The meta-analysis demonstrated a significant and robust effect on pain reduction (SMD = -0.61) and functional improvement (SMD = 0.52). These effects were largely maintained at 6- and 12-month follow-ups. Adverse events were rare and minor.

Physical Therapy/Structured Exercise: Five RCTs assessed structured physical therapy programs. The pooled analysis showed a significant effect on improving physical function (SMD = 0.58) and a moderate effect on pain reduction (SMD = -0.48).

3. Multimodal Interventions

Three high-quality RCTs evaluated intensive multimodal programs that combined physical therapy, psychological components (CBT or ACT), and patient education.

When compared to usual care or pharmacological monotherapy, these programs yielded the largest effect sizes for both pain reduction (SMD = -0.75) and functional improvement (SMD = 0.68).

Discussion

This systematic review and meta-analysis of 18 RCTs provides compelling evidence that non-pharmacological interventions, particularly structured psychological therapies and comprehensive multimodal programs, offer a superior long-term risk-benefit profile for the management of chronic non-cancer pain compared to pharmacological monotherapies. While opioids and NSAIDs can provide modest short-term analgesia, their benefits are often outweighed by a significant burden of adverse events and a lack of sustained efficacy. In contrast, interventions like CBT and physical therapy demonstrate durable improvements in both pain and function with minimal risk. The largest and most consistent benefits were observed in multimodal programs that integrate physical and psychological approaches, underscoring the value of a holistic, biopsychosocial model of care [19].

Comparison with Existing Literature: Our findings align with and extend previous research. The demonstrated efficacy of CBT is consistent with prior meta-analyses that have established it as a first-line treatment for various chronic pain conditions [13, 16]. Similarly, the finding that exercise and physical therapy improve function and reduce pain is well-supported [14, 20]. The key contribution of this review is the direct comparative synthesis. Our results echo the conclusions of large-scale clinical trials like the SPACE trial, which found that a 12-month course of opioid therapy was not superior to non-opioid medications for improving pain-related function [21]. Furthermore, our quantification of the high odds of adverse events with opioids (OR=3.15) reinforces warnings and guidelines from major public health

bodies, such as the Centers for Disease Control and Prevention (CDC) [9] and the UK's National Institute for Health and Care Excellence (NICE) [22], which advocate for non-pharmacological and non-opioid therapies as preferred first-line treatments.

Clinical and Policy Implications: The implications of these findings are significant. For clinicians, this review provides a strong evidence-based rationale to prioritize non-pharmacological therapies in the management of chronic pain. The initial treatment plan should emphasize patient education, active therapies like physical therapy, and psychological support like CBT. Pharmacological agents should be used judiciously, as adjuncts rather than monotherapies, for the shortest duration necessary, and after a thorough discussion of risks and benefits [23].

For healthcare systems and policymakers, these results highlight the need to improve access to and reimbursement for high-quality non-pharmacological treatments. The upfront cost of a 12-week CBT or physical therapy program may be higher than a monthly prescription, but the long-term benefits in terms of improved function, reduced healthcare utilization, and avoidance of medication-related harm likely represent a significant cost-saving [24, 25]. Investment in integrated, multidisciplinary pain clinics should be a public health priority [26].

Table 2: Summary of Meta-Analysis Findings

Outcome	Comparison	k (Studies)	N (Participants)	Effect Estimate (SMD or OR)	95% Confidence Interval	Heterogeneity (I^2)	p-value
Pain Reduction	Opioids vs. Placebo/Usual Care	4	1118	SMD = -0.55	-0.71 to -0.39	35%	<0.001
	NSAIDs vs. Placebo/PT	3	1200	SMD = -0.42	-0.59 to -0.25	0%	<0.001
	CBT vs. Control	6	1978	SMD = -0.61	-0.78 to -0.44	45%	<0.001
	PT/Exercise vs. Control	5	1498	SMD = -0.48	-0.65 to -0.31	52%	<0.001
	Multimodal vs. Control	3	1950	SMD = -0.75	-0.92 to -0.58	12%	<0.001
Functional Improvement	CBT vs. Control	6	1978	SMD = 0.52	0.38 to 0.66	28%	<0.001
	PT/Exercise vs. Control	5	1498	SMD = 0.58	0.40 to 0.76	30%	<0.001
	Multimodal vs. Control	3	1950	SMD = 0.68	0.51 to 0.85	5%	<0.001
Adverse Events	Opioids vs. Non-Pharmacological Interventions	4	1430	OR = 3.15	2.40 to 4.12	0%	<0.001

SMD = Standardized Mean Difference; OR = Odds Ratio; k = number of studies; N = total number of participants. A negative SMD favors the intervention for pain reduction. A positive SMD favors the intervention for functional improvement. An OR > 1 indicates higher odds of adverse events in the first-named group.

Strengths and Limitations: The primary strengths of this review include its comprehensive search strategy, adherence to rigorous PRISMA guidelines, inclusion of only RCTs, and use of meta-analysis to provide pooled effect estimates. However, several limitations must be acknowledged. First, the included studies were heterogeneous in terms of patient populations, intervention protocols, and outcome measures, which can impact the validity of pooled estimates. We used a random-effects model to account for this, but heterogeneity remained moderate in some analyses. Second, blinding is a major challenge in non-pharmacological trials, which increases the risk of performance and detection bias [27]. Third,

there is a potential for publication bias, where studies with negative or null findings are less likely to be published. Finally, our review was limited to English-language publications, which may have excluded relevant studies.

Directions for Future Research: Future research should focus on several key areas. Head-to-head RCTs with long-term follow-up are urgently needed to directly compare different active interventions (e.g., CBT vs. opioids; multimodal care vs. NSAIDs). Research should also move towards personalized pain medicine, investigating which patients are most likely to respond to specific interventions based on their clinical, psychological, and biomarker profiles (i.e., pain phenotyping) [28, 29]. Finally, implementation science research is crucial to understand how to best integrate effective non-pharmacological treatments into diverse clinical settings and overcome barriers to access [30].

Conclusion

In conclusion, this systematic review demonstrates that non-pharmacological and multimodal interventions provide more durable and safer outcomes for adult patients with chronic non-cancer pain than pharmacological monotherapies.

The evidence strongly supports a paradigm shift away from a medication-first approach towards an integrated, biopsychosocial model that empowers patients with self-management skills through therapies like CBT and physical therapy. Such an approach is better aligned with the long-term goals of improving function, enhancing quality of life, and minimizing harm.

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