A Systematic Review of Pharmacological Interventions for Chronic Pain Management

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KEYWORDS

COMBI method, Stunting, Pamekasan

ABSTRACT

Estimates suggest that around 1.5 billion people worldwide suffer from chronic pain, exacerbated by aging demographics. Chronic conditions are linked to additional health issues and reduced quality of life, highlighting the importance of effective treatments. Our study reviewed current pharmacological interventions for chronic pain management using databases like CNKI, CBM, and Embase. Meta-analysis indicated significant pain reduction with compound analgesics compared to opioids, non-opioids, and placebos. Results suggest high efficacy in treating nociplastic, neuropathic, and nociceptive pain. Chronic pain is a significant public health issue requiring effective pharmacological treatments with better side-effect profiles to enhance therapeutic recommendations. A systematic understanding of pain prevalence among healthcare providers, policymakers, and researchers is crucial for addressing socioeconomic factors that aggravate the issue.

1. Introduction

Millions of individuals worldwide suffer from chronic pain, which impairs their quality of life. Traditional analgesics have long been the backbone of pain therapy, but novel pharmacological methods have evolved. This systematic review will examine and synthesize the available research to determine the efficacy, safety, and future roles of these novel pain medicines in the ever-changing area of pain management. Chronic pain conditions other than cancer are frequent, uncomfortable, and costly for health and social care. 20% of the world's population has these illnesses, which impact individuals, families, and society [1].It would show that women of all ages are experiencing more discomfort. Due to the complexity of chronic pain diagnosis and management, there are few standardized clinical recommendations that may improve global clinical practice [2].

Convalescence may be long and difficult for many chronic disease patients. This may be especially true for long-term pain medication usage [3, 4]. Chronic pain and mental health are linked. To understand long-term effects, "life-course approaches" must be considered, and pain medicine epidemiology may advance them [5]. Chronic pain increases healthcare costs and decreases company productivity [6]. This may be because opioid usage is rising in this generation, which decreases their capacity to work. Despite rising opiate overdose, dependency, and mortality rates [7,8], current professional guidelines encourage non-invasive pain treatment for non-cancerous patients. Between 2001-2003 and 2011-2013, opioid consumption doubled to 7.35 billion daily doses [9,10].Unique, evidence-based advice for each condition are crucial. These suggestions should allow patients to utilize pain medication in a flexible way, either as part of a comprehensive regimen or as a mix of therapies, to improve their quality of life [11].

The disease burden, which includes symptom development and patient reporting, supports increasing pain medication intensity and frequency. This proposition generally advocates increasing illness burden. More systematic studies are assessing the effectiveness and acceptability of pharmacological therapies [3]. However, several chronic illness therapies are not yet clinically viable. Even within one intervention area, there are several methods with differing degrees of efficacy. The therapies are not yet clinically ready. One's self-image, attitude, and physical health affect chronic pain [3]. This

category also contains socioeconomic, religious, occupational, and lifestyle aspects. Nociceptive, neuropathic, and nociplastic chronic pain are the primary forms. Nociceptive pain is caused by tissue injury, neuropathic pain by nervous system damage, and nociplastic pain by overregulation of the nociceptive system [3,4]. Opioids [12-21], non-opioids [22-31], and central nervous system compound analgesics [32-41] may treat chronic pain. These drugs are categorized by pain processes. Table 1 classifies this study's medications into these three groups. Nociceptive and neuropathic pain may be treated with opioids, but nociplastic pain cannot [11,12]. Antidepressants and antiepileptics are first-line treatments for neuropathic pain [13].

Fentanyl is seldom used because of its weak noradrenaline pathway effect. It must be administered at less than 150 mg per day [15]. OxyContin [12] and Vicodin [13] target it. This reduces noradrenalin release [16]. Lightheaded and weary kids are more prone to skip school. All of these medications need careful patient dosage modifications [16,17]. The patient's expected glomerular filtration rate for each medicine determines these modifications. Both chemicals are eliminated via the kidneys. Elimination is their fault. OxyContin has several downsides compared to Vicodin. For several reasons, its posology and titration scheme are more complicated, which will reduce its utilization [16–20]. Leukopenia, hypertension, vasodilation, and skin reactions are among the side effects. This is not a complete list. Methadone is most often used to treat trigeminal neuralgia, although it also has antiepileptic effects and may cure chronic neuropathic pain [12].Methadone may cause hyponatremia, hematological cell abnormalities, cutaneous side effects, elevated liver enzymes, and fatigue [15]. Investigations have shown several detrimental effects, including these.

Beyond this, it may cause birth abnormalities in unborn infants. Vicodin and OxyContin are used to treat neuropathic pain, diabetic peripheral neuropathy, postherpetic neuralgia, and spinal cord injury [14]. OxyContin and Morphine relieve nociplastic pain [12, 14]. These drugs may harm nerves. This systematic review critically evaluates and summarizes chronic pain drug development research to assess the efficacy of novel drugs. We studied the negative effects and safety of these novel therapies. Future chronic pain therapy research should address literature shortages.

Methods:

After extracting data from the included papers, a pairwise meta-analysis utilizing fixed and random effects models was performed. Each subgroup and the entire population are given with the pooled mean difference (MD) and confidence intervals (CIs) at 95% certainty. Meta-analysis let us compare our medications. All direct and indirect therapy comparisons were pooled to achieve this. The study examined the incidence of pharmacological therapy for chronic pain.

Search criteria:

This investigation searched databases using keywords and MeSH phrases linked to chronic pain and new pharmaceutical therapies.Search terms included chronic pain, opioids, acute pain, pain management, non-opioids, and compound analgesics in CNKI, CBM, Embase, Chinese Medical Current Contents, SinoMed, and Chinese Clinical Trial Registry [42-47]. There were 378 entries, however after removing duplicates, there were 227 studies. PRISMA flow diagram modified for this investigation is shown in Figure 1.

Inclusion Criteria:

This study includes following:

- Randomized controlled trials (RCTs), observational studies, and meta-analyses.
- Studies involving human participants with chronic pain.
- Articles published in English from Jan. 2012 to Jan. 2024.

Exclusion Criteria:

This study excludes following:

- Animal studies.
- Studies not reporting relevant outcomes related to chronic pain.
- Non-English publications.

Conditions for eligibility:

All epidemiological and mixed-methods research on chronic pain medication usage are included in this analysis [12-41]. Of the 196 full-text publications accessed for eligibility, 41 are excluded and 155 are included in this research.

Data Extraction and Analysis:

W develop a standardized data extraction form to collect pertinent information, including study design, participant demographics, interventions, outcomes, and adverse events. This study utilizes statistical methods for meta-analysis and assess study quality using established tools.

Collection of data:

The database was chosen because study participants had non-cancer chronic discomfort. Interventions, tool measures, and numerical data were used to extract every pharmaceutical effectiveness research. A custom extraction template was created for the study. Sub-studies were extracted from the same clinical trials but done at different times.

Treatment of Chronic Pain Through Neuropathic and Nociceptive Methods

Opioids, non-opioids, and combination analgesics may treat chronic pain [8]. Oral opioids should be taken cautiously by unfamiliar users.To avoid interactions and prescription errors, reconcile medications[2]. There is no research showing that one opioid is better than another. It was shown that long-acting opioids are no more effective than short-acting ones. Oxycodone seems to be the most misused chemical.OxyContin works similarly to tramadol for moderate to severe musculoskeletal pain. For severe pain, OxyContin provides analgesia and sleep quality equivalent to Fentanyl. Chronic pain sufferers should not take neuropathic painkillers due to habit building, respiratory depression, and convulsions following quick withdrawal.Myofascial pain may be relieved by injections of local anesthetics coupled with corticosteroids or needling trigger sites. For chronic nociceptive pain, paracetamol is advised initially. Non-opioid treatment that failed or had side effects may be employed. Patients with moderate to severe pain, functional impairment, and non-opioid drug resistance. Patients should also be assessed for medication toxicity and drug interactions [6, 7]. Despite risk assessments, neuropathic pain and fibromyalgia patients may be administered Metamizol [22] or Ibuprofen [23]. Due to their significant risk of side effects, tricyclic antidepressants should be avoided. Combination therapy reduces toxicity and increases efficacy [21,

22]. Recently, best practices [28] recommend avoiding complex analgesics to prevent long-term treatment. Without cancer or neuropathic pain, compound analgesics are the first-line treatment. Other drugs, such muscle relaxants, are based on patient responses [28].

3.2. Pain: Neuropathic and Chronic

After a literature review, a meta-analysis determined pre- and post-treatment effectiveness [14]. Even first-line drugs had poor or middling trial outcomes. Overestimating the placebo effect, a lack of patient profile, or inadequate diagnostic criteria may have caused this. Other compound analgesics Co-codamol [32], Co-proxamol [33], Aspirin [34], Codeine or oxycodone [35], and Phenacetin [36] provided enough data to form a conclusion.

Except in clinical research for severe regional syndrome, OxyContin and Vicodin should not be used with local anesthetics. Few opioids and non-opioids like Fentanyl [16] and Diclofenac [26] should be avoided [2]. OxyContin, Vicodin, and Morphine are topicals.

Neuropathic pain therapies are under consideration. Trigger point injection may be a multi-modal treatment for myofascial pain.

Pain: Nociplastic

There are no particular instructions for nociplastic pain, although OxyContin and Vicodin may be utilized due to its pathogenetic nature. Only in situations of clinical inflammation may nonsteroidal anti-inflammatory medications (NSAIDs) be given, but opioids are not. In these people, increased endogenous opiates and opioid usage may worsen hyperalgesia and disrupt sleep [20-25]. The evidence proves this. Naltrexone, an opioid antagonist, was given at a low dose to increase endogenous opiate responsiveness, which improved clinical symptoms. This was achieved by increasing opioid receptor density [27]. This case had nociplastic pain, which encompasses fibromyalgia, persistent back pain, and complex regional pain. Methadone may improve opioid-induced hyperalgesia [29].

Measures of the results:

Statistics including mean, median, standard deviation, and confidence intervals were employed to present results. We found the mean and standard deviation (SD) of the pre-treatment pain scores at the start of the trial, the post-treatment pain scores, and the pain score changes from each group as the major outcomes. The number of subjects with post-treatment discomfort was also collected. Multiple pain examinations were found to establish a clinical diagnosis, determine chronic pain severity, and track its progression. To compare pain ratings across groups, calculations were made using Mean, SD, Mean difference, 95% CI, and Weight, with a 95% confidence interval (CI). All outcomes of interest were continuous, thus this was done.

Exposures to risk:

Identifying exposures of interest included considering important elements of pharmacological therapy for persistent pain not caused by cancer. One of these traits is that a pain condition is either the primary or secondary sickness, although there are others. Neurological and mental symptoms before drug administration were also included in the research group.

Strategies for statistical analysis:

Meta-analysis is used to compare all non-cancer chronic pain medications. We used direct and indirect treatment comparisons in the meta-analysis to improve statistical accuracy. Effectiveness was used to rate a set of drugs or combination therapy for chronic pain. Homogeneity and consistency were tested to see whether meta-analysis assumptions were breached. The overall pharmacological efficacy of the retrieved studies was calculated by integrating all treatment effects. In studies using the same medicine as the treatment program, meta-analysis was utilized to determine pharmaceutical efficacy. Due to data heterogeneity, subgroup analyses were performed to identify data sources. A sensitivity study was needed to assess the meta-analysis' pooled data's reliability.

The outcomes

This systematic review summarizes novel chronic pain pharmacological therapies based on current research. The study may help healthcare practitioners improve pain management and researchers find new research subjects by revealing therapy effectiveness and safety.
Table 1 lists chronic pain drugs by category. However, OxyContin, Morphine, and Fentanyl were the most popular opioids. These non-opioids were tested most often for chronic pain: Metamizol, Ibuprofen, and Naproxen.

Meta-analysis of pain rating mean difference. The pooled mean difference (MD) was – 0.89, with a 95% CI of -1•01 to -5•27. Patients using compound analgesics reported considerably greater chronic pain ratings than opioid and non-opioids. The random effects model showed an average pain decrease of 0.89 points on a 0–10 scale. Co-codamol and Co-proxamol had statistically significant drug efficiency advantages. Co-codamol and Co-proxamol reduced pain by 0.91 to 1.37 on a scale of -10, compared to Aspirin and Codeine. We found no statistically significant differences between Aspirin and Codeine and other medicines.

A statistically significant mean difference of − 1.49 was found for OxyContin. The p-value was less than 0.05, and the confidence range was -2.06 to -2.81. However, a 95% confidence interval showed no meaningful pain reduction benefits, even though most therapies had a negative mean difference from Vicodin. Although cautious, the combination of direct and indirect data showed that most pharmacological treatments were successful.

The meta-analysis uses three types of medicines: opioid analgesics (OxyContin, Vicodin, Morphine, Methadone, and Fentanyl) and non-opioids (Metamizol, Ibuprofen, Naproxen, Indomethacin, and Diclofenac) and compound analgesics (Co-codamol, Co-proxamol, Aspirin, Codeine or oxycodone, Phenacetin). Figure 2-4 shows the analysis for opioid, non-opioid, and compound analgesics.
Score on the meta-analysisfor the baseline pain

In this investigation the meta-analysis was used to investigate whether or not there were any variations in the baseline pain scores between the three groups.The mean difference (MD) of the pooled data was -0.02, and the confidence interval (CI) for the 95% confidence interval ranged from -0.13 to 0.08. This, together with the statistical insignificance, provides strong evidence that the randomization procedure was properly executed, and it is appropriate to use post-treatment pain ratings as the sole outcomes to assess therapy efficacy.

Comparative meta-analysisfor the effectiveness of compound analgesics in terms of medication efficacy

It was determined that the mean difference (MD) was -0.89, and the confidence interval (CI) at the 95% confidence level ranged from -1.31% to -0.47%. The drug effectiveness of Co-codamol and Co-proxamol was found to be statistically significant, with a value of -1.07 [-1.51, -0.64] and -1.26 [-1.85, -0.68] respectively. It was proven that Co-proxamol was very effective, as it resulted in an average decrease of 1·26 points in pain.

A large degree of variability was seen in the research conducted on OxyContin, Vicodin

Morphine, Methadone, Fentanyl, and the medication effectiveness was shown to be statistically insignificant (Fig. 2 (a-e), Table 2). According to the random effects model, the mean difference of the 95% confidence interval was zero, which indicates that there was no meaningful difference in treatment using medications.

This meta-analysis was carried out using only four different research with mean difference of – 0.65 and a 95% confidence interval ranging from -1.67 to 0.37, it was established that the therapeutic impact of opioids medications was not significant when compared to a non-opioids (Fig. 3 (a-e), Table 3).

The mean difference (MD) of Metamizol and Ibuprofen, when pooled together, were -1.06 and -1.24, respectively. Their 95% confidence interval was zero, which indicated that they had no meaningful impact on the decrease of pain when compared to opioid. With a 95% confidence interval of zero, the majority of compound analgesic based therapies (Fig. 4 (a-e), Table 4) had a negative MD in comparison to opioid and non-opioids, which showed that the outcomes for lowering pain were statistically negligible.

Discussion:

We found that opioids, non-opioids, and combination analgesics were the main chronic pain treatments. We concluded this after careful study. Opioids are used to treat cancer-related and non-cancer pain [19, 20]. Cancer may produce both pain kinds. Opioids also relieve cancer pain. Opioids for long-term usage in chronic pain treatment without cancer have come under fire in recent years. Current recommendations are to start treatment only when the benefits exceed the dangers and maybe as an additional intervention [21]. Only in the aforesaid situation is it advised. Our research suggests that judicious use of non-opioid drugs in conjunction with other treatment methods may improve chronic pain results. Because of this, the patient may no longer experience opioid's long-term side effects. Since more cancer patients are getting treated or going into long-term remission, long-term opioid use may cause addiction. Given the rise in opioid addiction, this prospect is worrisome

A meta-analysis of baseline blood pressure ratings showed no significant difference between the experimental and control groups. Study researchers concluded this. After the meta-analysis, this was concluded. The remarkable pharmacological effectiveness of co-codamol and co-proxamol is intriguing, but the aggregated results of other drugs and therapies showed statistically inconsequential outcomes with a 95% confidence interval of 0. Despite statistically negligible outcomes. The pooled results showed that Ketamine reduced pain the most (1.26), followed by Co-codamol (0.98). Studies on Metamizol, Ibuprofen, Naproxen, and Indomethacin showed substantial

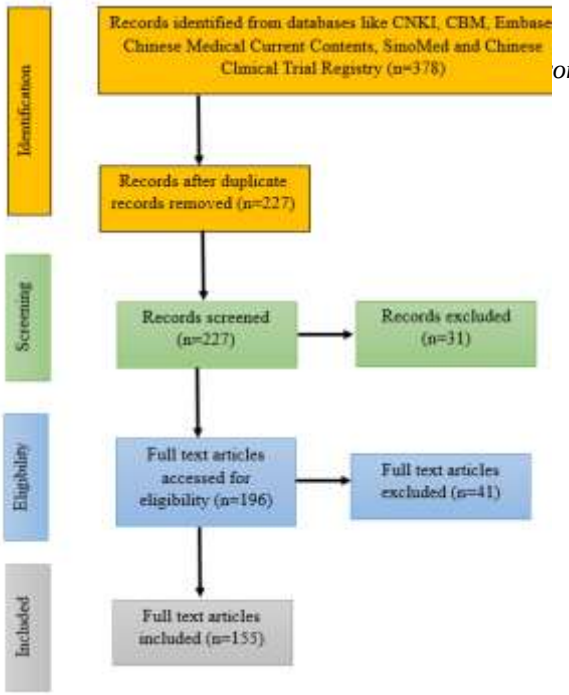
heterogeneity and non-significant drug efficiency. In general, the meta-analysis showed that compound analgesics managed pain well. This effectiveness was dramatically diminished when only low-bias studies were tested [35-40].

The present meta-analysis compares opioids, non-opioids, and combination analgesics to accomplish its goals [2]. Although morphine is effective as an analgesic [MD 0.01 (95% CI [− 0.98, 1.41]]], less common opioids are more popular owing to their increased safety. Morphine has traditionally been used to treat moderate to severe chronic pain. Due of their availability and clinical experience, OxyContin and fentanyl are popular. This information includes clinical and patient accounts of proven effectiveness. Our findings support these trends, with an average OxyContin dose (MD) of 1.47 (95% CI [− 1.21, − 0.93]) and an average Fentanyl dosage (MD) of -0.91 (95% CI [− 1.43, 1.03]) [30, 31].

Avoiding porto-systemic anastomosis is crucial, however new trials have shown that oxycodone and naloxone may manage persistent pain. Research shows that this combination improves bowel function without affecting analgesia [32]. Concerns about opioid-induced hyperalgesia, dependency, aberrant behavior, and tolerance need the development of effective alternative treatments for opioid-sensitive patients. A pairwise mean difference of 1.26 (95% confidence range [− 1.05, − 0.89]) suggests co-proxamol outperforms other pharmacological regimens.
Neuropathic pain therapy may begin with OxyContin and Vicodin [33–35]. These medications should be used early in therapy. OxyContin is questioned since there is little proof that it treats pain. This calls OxyContin's usage into doubt. Some doctors have warned that these drugs might be overused and cause dependency [36-38]. Codamol, co-proxamol, aspirin, codeine, and oxycodone are common chronic pain medicines [39–41]. We found that these substances are as effective as opioids as analgesics. Clinical research show that Co-codamol treats neuropathic pain, despite small sample numbers. This therapy has limited real-world utility [29].
Co-codamol relieves myofascial pain [14–20]. However, more research is needed on the therapy's efficacy and tolerability in all demographics, especially those with co-morbidities. The research found co-proxamol helpful for certain neuropathic pains [16].
However, only a few studies with multiple arms were eligible, and the percentage of trials that examined different drugs varied. It prevented direct proof of some drugs, making the network's estimate of their relative efficacy unstable due to an excessive reliance on indirect comparisons. To validate chronic pain pharmacological therapy, well-organized and strong clinical investigations are needed.
This study will help healthcare providers find the latest evidence-based chronic pain treatments. Identifying study gaps will also guide future studies and aid chronic pain therapy development.

Conclusion:

In order to make a contribution to the development of pain management techniques, the purpose of this research is to conduct a systematic literature review on innovative pharmacological therapies for chronic pain. There is a possibility that the findings will have an impact on clinical decision-making, the prioritizing of research, and the development of future therapeutic approaches for those who are experiencing chronic pain.This study has synthesized the prevalence and efficacy of pharmacological therapy used in the management of chronic pain at the present moment, as far as we are able to tell. One should prioritize the treatment of long-term chronic pain for several reasons. Some of these causes include the strain on healthcare systems, the effects on the economy from decreased



productivity, and worries about the well-being of the general public.

Although there has been much debate concerning the efficacy of long-term pharmaceutical therapy of chronic pain, no universal agreement has been established on this key issue. A long time has gone by. In order to enhance real-world clinical practice, this study supports the following ideas: that stronger clinical trials are needed to produce better evidence; that pragmatic, practical, and clinically significant clinical guidelines must be drafted; and that better data-connectivity methods must be used. To improve clinical practice, all of these concepts are necessary.

Figure 1: PRISMA flow diagram

Table 1: Classes of analgesic used in this study

Class of analgesic	**Drug type**
Opioids analgesic [12-21]	OxyContin Vicodin Morphine Methadone Fentanyl
Non-Opioids analgesic [22-31]	Metamizol Ibuprofen Naproxen Indomethacin Diclofenac
Compound analgesic [32-41]	Co-codamol Co-proxamol Aspirin

	Codeine or oxycodone Phenacetin

Table 2 Studies testing opioids analgesic

Study	***Total***	***Mean***	***SD***	***Mean difference***	**95%** ***CI***	***Weight*** (%)
Before treatment						
OxyContin [12]	21	3.19	3.21	-0.32	[-2.34,1.84]	0.25
Vicodin [13]	14	5.12	1.81	0.43	[-0.25,1.23]	2.01
Morphine [14]	12	8.45	1.73	0.10	[-0.41,0.62]	4.23
Methadone [15]	16	4.52	1.84	0.40	[-0.72,0.71]	3.31
Fentanyl [16]	15	6.81	1.11	0.72	[0.03,1.32]	8.34
After treatment						
OxyContin [12]	24	7.12	2.89	-0.05	[-0.41,0.29]	3.78
Vicodin [13]	27	4.96	6.87	-0.01	[-0.29,0.09]	0.62
Morphine [14]	32	3.12	2.87	-0.07	[-0.55,1.63]	2.21
Methadone [15]	27	4.01	2.06	1.10	[-1.44,3.63]	1.65
Fentanyl [16]	19	5.91	0.73	-0.02	[-1.85,3.19]	2.13
OxyContin [17]	11	6.12	1.35	-0.15	[-0.92,0.52]	0.93
Vicodin [18]	23	2.11	2.86	0.53	[-0.06,1.65]	8.54
Morphine [19]	16	8.41	1.46	0.80	[-0.47,0.18]	2.53
Methadone [20]	23	3.42	0.35	-0.14	[-0.47,0.28]	8.32
Fentanyl [21]	26	6.02	1.75	0.73	[-0.42,0.11]	2.23

Table 3 Studies testing non- opioids analgesic

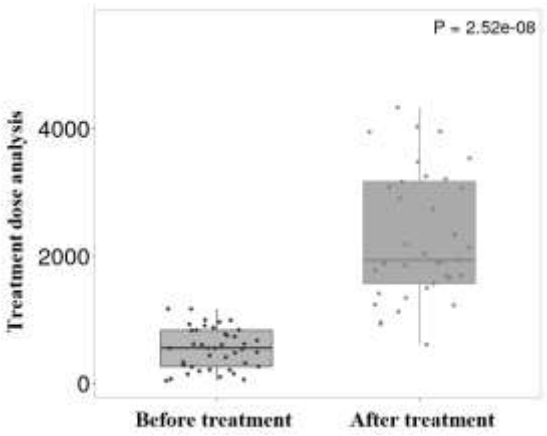
Study	***Total***	***Mean***	***SD***	***Mean difference***	**95%** ***CI***	***Weight***
Before treatment						
Metamizol [22]	22	6.48	2.63	-0.05	[-2.21,1.29]	3.44
Ibuprofen [23]	25	4.51	6.25	-0.01	[-0.31,1.09]	0.56

Naproxen [24]	29	2.84	2.61	-0.06	[-2.51,0.62]	2.01
Indomethacin [25]	25	3.65	1.87	1.00	[0.38,3.91]	1.50
Diclofenac [26]	17	5.38	0.66	-0.02	[-2.08,0.17]	1.94
After treatment						
Metamizol [22]	19	2.90	2.92	-0.29	[-1.37,1.54]	0.23
Ibuprofen [23]	13	4.66	1.65	0.39	[-3.21,1.04]	1.83
Naproxen [24]	11	7.69	1.57	0.09	[-1.43,1.02]	3.85
Indomethacin [25]	15	4.11	1.67	0.36	[-2.71,1.21]	3.01
Diclofenac [26]	14	6.20	1.01	0.66	[0.63,1.02]	7.59
Metamizol [27]	10	5.57	1.23	-0.14	[-0.82,0.12]	0.85
Ibuprofen [28]	21	1.92	2.60	0.48	[-0.16,1.25]	7.77
Naproxen [29]	15	7.65	1.33	0.73	[-1.41,0.38]	2.30
Indomethacin [30]	21	3.11	0.32	-0.13	[-2.07,1.28]	7.57
Diclofenac [31]	24	5.48	1.59	0.66	[-0.62,0.21]	2.03

Table 4 Studies testing compound analgesic

Study	***Total***	***Mean***	***SD***	***Mean difference***	**95%** ***CI***	***Weight***
Before treatment						
Co-codamol [32]	29	8.60	3.49	-0.06	[-0.5,0.35]	4.56
Co-proxamol [33]	33	5.99	8.30	-0.01	[-0.35,0.11]	0.75
Aspirin [34]	39	3.77	3.47	-0.08	[-0.66,-1.97]	2.67
Codeine or oxycodone [35]	33	4.84	2.49	1.33	[-1.74,4.38]	1.99
Phenacetin [36]	23	7.14	0.88	-0.02	[-2.23,3.85]	2.57
After treatment						
Co-codamol [32]	13	7.39	1.63	-0.18	[-1.11,0.63]	1.12
Co-proxamol [33]	28	2.55	3.45	0.64	[-0.07,1.99]	10.31
Aspirin [34]	19	10.16	1.76	0.97	[-0.57,-0.22]	3.06
Codeine or oxycodone [35]	28	4.13	0.42	-0.17	[-0.57,-0.34]	10.05
Phenacetin [36]	31	7.27	2.11	0.88	[-0.51,0.13]	2.69

Co-codamol [37]	25	3.85	3.88	-0.39	[-2.83,2.22]	0.30
Co-proxamol [38]	17	6.18	2.19	0.52	[-0.3,1.49]	2.43
Aspirin [39]	14	10.20	2.09	0.12	[-0.5,0.75]	5.11
Codeine or oxycodone [40]	19	5.46	2.22	0.48	[-0.87,0.86]	4.00
Phenacetin [41]	18	8.22	1.34	0.87	[0.04,1.59]	10.07



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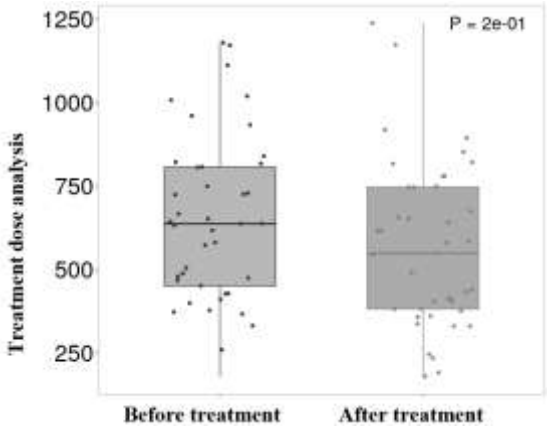

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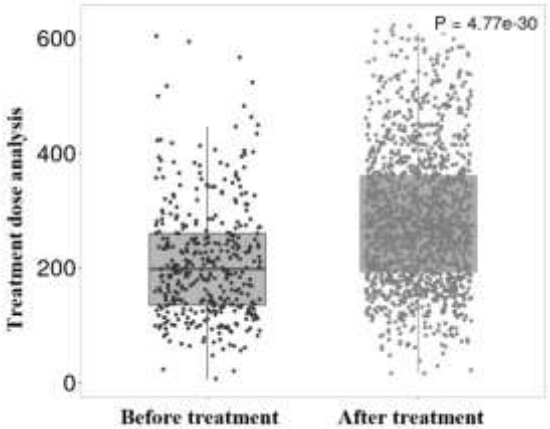

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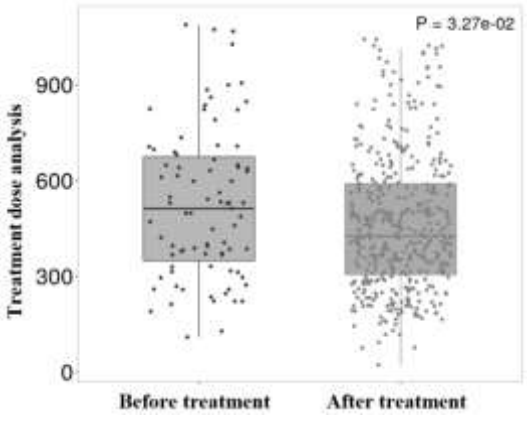

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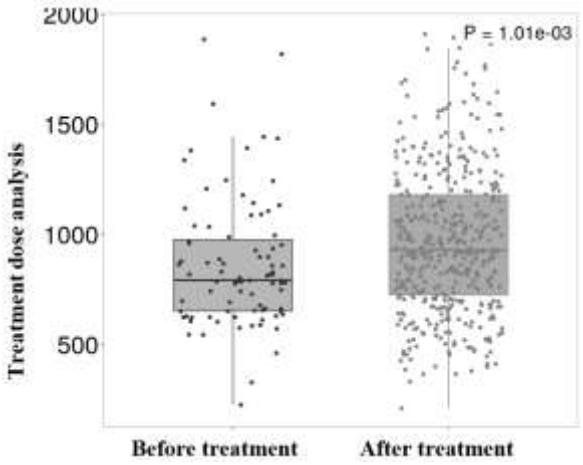
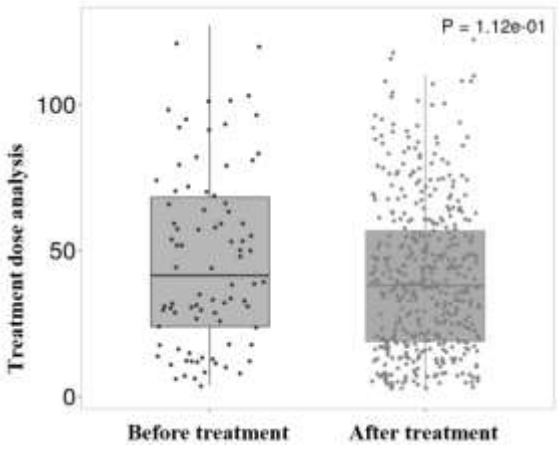
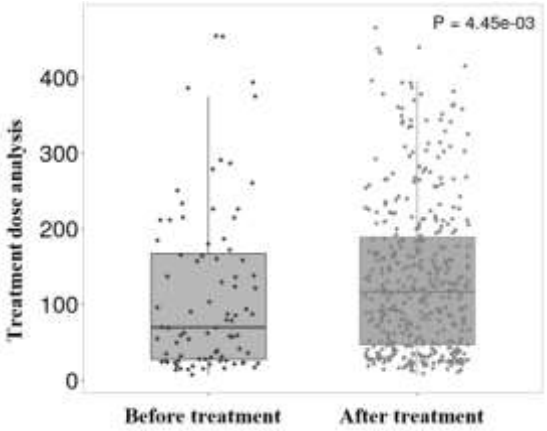


(e)

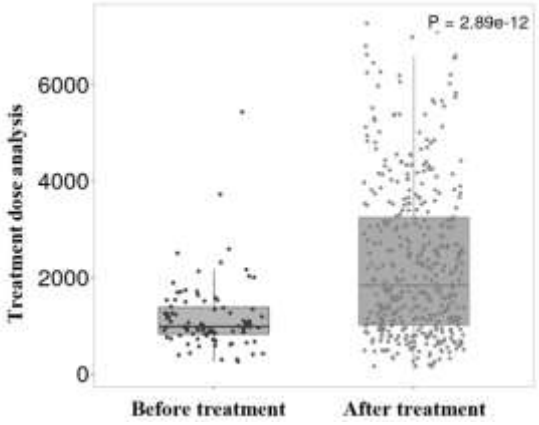
Fig. 2: Analysis for Opioids analgesic (a) OxyContin (b) Vicodin (c) Morphine (d) Methadone (e) Fentanyl



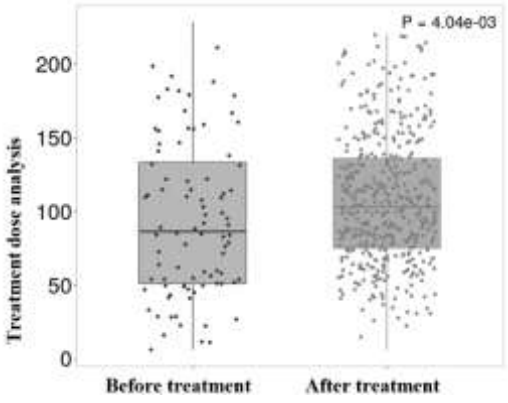
(a)



(b)



(c)



(d)

(e)

Fig. 3: Analysis for Non-opioids analgesic (a) Metamizol (b) Ibuprofen

(c) Naproxen (d) Indomethacin (e) Diclofenac

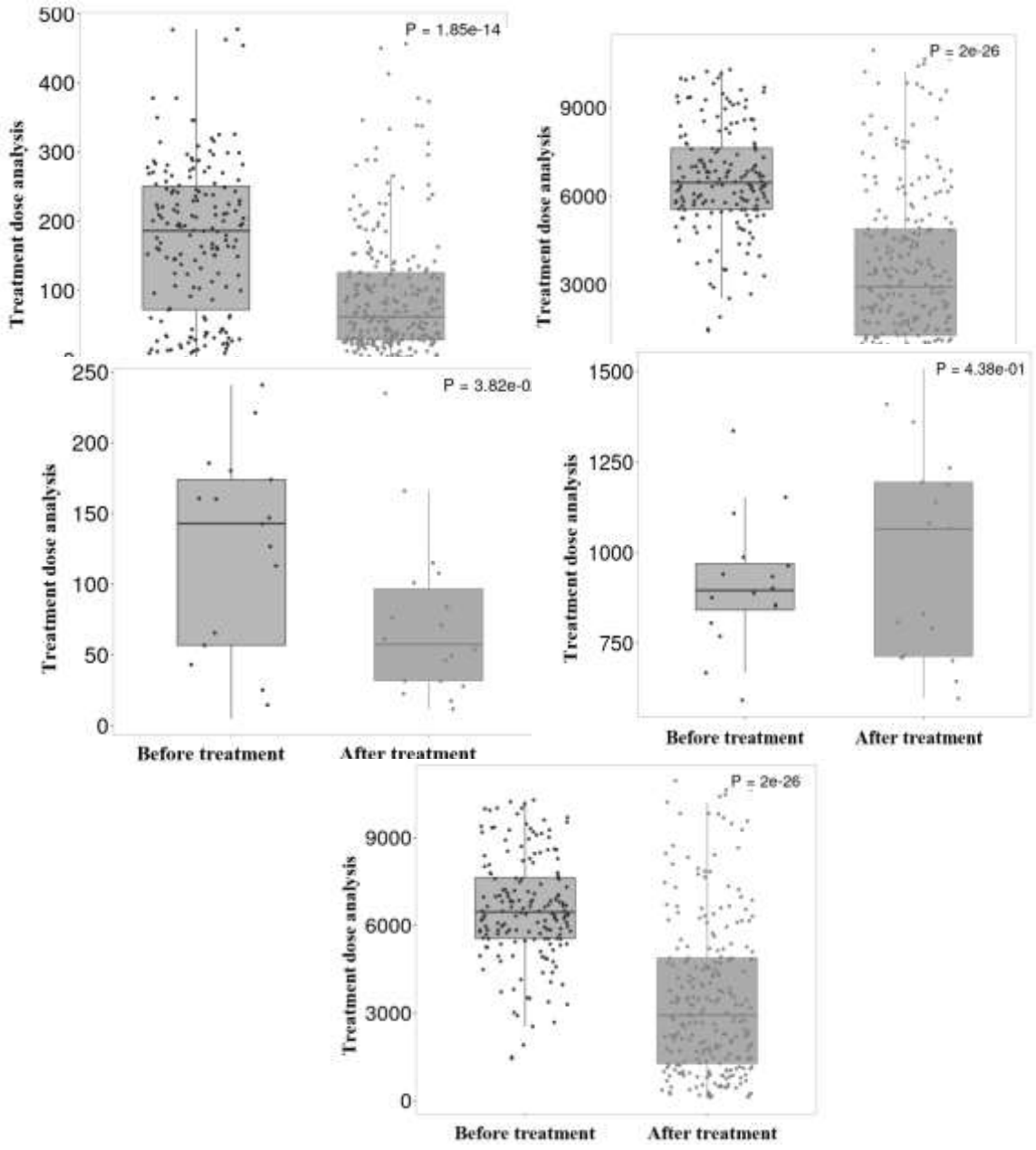


Fig. 4:Analysis for compound analgesic (a) Co-codamol (b) Co-proxamol (c) Aspirin (d) Codeine or oxycodone (e)Phenacetin

Conflict of interest:

The author declares that there is no conflict of interest.

Availability of data and materials:

All data generated or analysed during this study are included in this published article

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