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Review Article

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NEUROPATHIC PAIN SECTION

Effect of Combined Diclofenac and B Vitamins (Thiamine, Pyridoxine, and Cyanocobalamin) for Low Back Pain Management: Systematic Review and Meta-analysis

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Abstract

Background. Cumulative evidence suggests an analgesic effect of thiamine, pyridoxine, and cyanocobalamin (TPC) in monotherapy, and also when combined with nonsteroidal anti-inflammatory drugs (NSAIDs), particularly diclofenac, in a synergistic manner. The aim of this review was to determine the effects of diclofenac combined with TPC compared with diclofenac monotherapy for low back pain (LBP) management. **Methods.** We searched for randomized clinical trials on the MEDLINE, EMBASE, LILACS, and Cochrane databases of records of clinical trials, among other sources. We evaluated the risk of bias regarding randomization, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. A random-effects meta-analysis to examine patients with acute LBP (N = 1,108 adults) was performed, along with a subsequent sensitivity analysis. **Results.** Five studies in patients with LBP were included in the qualitative synthesis. Four of these studies in acute LBP were included in the first meta-analysis. A sensitivity test based on risk of bias (three moderate- to high-quality studies) found that the combination therapy of diclofenac plus TPC was associated with a significant reduction in the duration of treatment (around 50%) compared with diclofenac monotherapy (odds ratio = 2.23, 95% confidence interval = 1.59 to 3.13, $P < 0.00001$). We found no differences in the safety profile and patient satisfaction. **Conclusions.** This meta-analysis demonstrated that combination therapy of diclofenac with TPC might have an analgesic superiority compared with diclofenac monotherapy in acute LBP. However, there is not enough evidence to recommend this therapy in other types of pain due to the scarcity of high-quality studies.

Key Words: Back Pain; Diclofenac; B Vitamins; Systematic Review; Meta-analysis

Introduction

Low back pain (LBP) is a serious and widespread public health problem. In fact, several reports indicate that global prevalence of LBP in adults is approximately 12%, whereas the one-year prevalence is 38% and lifetime prevalence is around 40% [1]. Due to the increase of several comorbidities, such as obesity, smoking, sedentary lifestyles, and aging in the general population, recent reports suggest that this prevalence may rise [2,3]. In a survey of adult farmers in Saskatchewan, 84% of participants reported having experienced at least one episode of back pain during their lifetime [4]. In 2002, the US

National Health Interview Study reported that 26.4% of the 30,000 participants had experienced at least one full day of back pain in the last three months [5]. In addition, it has been estimated that the incidence of recurring back pain varies between 24% and 80% [6].

Although most patients with acute LBP improve with usual treatment, some have periods of relapse and develop chronic LBP [6]. In this context, anatomical (i.e., degenerative spinal conditions, muscle atrophy) and functional changes in the central nervous system (i.e., central sensitization) [7–9] have been described.

Thus, LBP is a frequent cause of persistent and/or significant disability. The Global Burden of Disease Study stated that back (and cervical) pain and migraines are among the leading causes of disability in the world [10]. Among more than 300 disorders analyzed in the study, back pain and cervical pain were the leading causes of disability worldwide over the last 25 years, affecting both high- and low-income countries, particularly the working population between 25 and 65 years of age [10].

Treatment for LBP involves pharmacological and nonpharmacological measures. Firstline drug treatment for LBP typically consists of the use of acetaminophen (paracetamol) or NSAIDs, but their use is limited by adverse gastrointestinal, renal, hepatic, and cardiovascular reactions, among others [11]. Adjuvant analgesics are drugs with indications other than pain that have analgesic properties in some painful conditions [12]. These drugs can exert a synergistic effect when combined with classical analgesic drugs. Some adjuvant drugs are used for the management of acute back pain, including benzodiazepines, cyclobenzaprine, methocarbamol, carisoprodol, baclofen, and tizanidine [11]. However, the use of these drugs is limited by their potential to cause sedation, dizziness, dependence and abuse (benzodiazepines and carisoprodol), hepatic toxicity, and multiple drug interactions [11]. In terms of opioid agonists, because most previous studies have been carried out in patients with chronic LBP, they are not considered to be firstline drugs for the management of the acute condition [11]. Likewise, these drugs carry a major risk of toxicity that includes adverse effects such as sedation, confusion, nausea, constipation, respiratory depression, tolerance, dependence, and potential for abuse [13]. Nonpharmacological approaches encompass psychological therapies, multidisciplinary rehabilitation, osteopathy, acupuncture, massage, physical activity, and various physical modalities with variable results (low- and moderate-quality evidence) [14]. Because there is currently no ideal treatment for LBP, the use of adjuvants that help to reduce the dose or duration of treatment with NSAIDs must be considered, as adjuvants can decrease disability in these patients.

For nearly 30 years, the analgesic effects of thiamine (vitamin B1), pyridoxine (vitamin B6), and cyanocobalamin (vitamin B12; TPC) have been studied at therapeutic doses (far higher than nutritional ones), as well as in combination with NSAIDs (particularly diclofenac), in patients with LBP [15–17]. The analgesic effect of TPC has been explained by multiple mechanisms of action, including an anti-inflammatory and antioxidant effect, the activation of adenosine receptors, the modulation of voltage-gated sodium channels (thiamine), blocking of P2X receptors by ATP (pyridoxine), and a GABAergic and serotoninergic effect (cyanocobalamin and pyridoxine), as well as other neurotransmitter systems [18–27]. Recent evidence indicates that potentiation of antinociceptive effects of morphine by B vitamins could be explained through intracellular pathways related to morphine tolerance (p-NR1 and p-PKC) and immunomodulatory effects in the spinal cord (IBA1 and IL-1β) [28]. Anti-inflammatory effects of B vitamins have been described in animal models of pain such as mechanical allodynia and neuropathic pain [29,30].

Regarding management of back pain with NSAID monotherapy vs NSAIDs combined with TPC, the most recently published systematic review concluded that the evidence was inconclusive, and a meta-analysis was not carried out [31]. Although the three studies included by Roelofs et al. reported positive results for combination therapy [31], there were only statistically significant differences in one of them [15]. However, the authors didn't include a randomized clinical trial (RCT) with a sample of 372 patients with acute LBP, which was published after their systematic review [32]. We hypothesize that the inclusion of this study might change the overall effects of the intervention in patients with LBP.

The aim of this systematic review and meta-analysis is to assess clinical evidence about the efficacy and safety of TPC combined with diclofenac for LBP pain treatment regarding pain relief, participant satisfaction, and adverse events.

Methods

We compiled all available published and unpublished evidence and used premature discontinuation of medication due to complete pain relief as the primary outcome measure. Secondary outcomes included decreased pain intensity according to a visual analog scale (VAS) measure, the occurrence of adverse events (i.e., gastrointestinal events), and participant satisfaction, based on the number of patients who described subjective improvement at the end of the study. We assessed the quality of the obtained results using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [33].

Data Sources and Search Strategy

We conducted this systematic review of RCTs in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses declaration criteria and the current recommendations of the Cochrane Collaboration [34,35]. We carried out searches up to June 2018 using the search terms "pain," "thiamine," "vitamin B1,"

"pyridoxine," "vitamin B6," "cyanocobalamin," "vitamin B12," "vitamin B complex," "Neurobion," and "diclofenac" in the following databases: MEDLINE (Ovid SP), Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE (Ovid SP), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Latin American and Caribbean Health Science Information Database (LILACS), International Standard Randomized Controlled Trial Registry (ISRCTN), ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP). No language, date of publication, or completion status filters were used. In addition, we carried out a search of the references for review articles, relevant clinical trials, textbooks, and conference summaries to identify more RCTs. In all cases, we read the full-text versions of these articles. We systematically contacted the corresponding authors by e-mail if the publication contained incomplete data (i.e., data on adverse events). Although the focus of this review is LBP, we searched for pain in general, with the intention of increasing the sensitivity of the search strategy, considering that there are a lot of terms with the same meaning (i.e., back pain, lumbago, spine pain, sciatica, and dorsalgia, among others).

The search equation is found in Appendix 1. Likewise, we made additional efforts to identify RCTs that were potentially relevant to the topic using the following data sources: 1) gray literature (theses, internal reports, non-peer-reviewed journals) and 2) other unpublished sources known to experts in the specialty (obtained via personal communication).

Study Selection

We included all RCTs that were performed in patients of any age suffering from LBP that was acute or chronic; primary or secondary; of mild, moderate, or severe intensity; and nociceptive, neuropathic, or nociplastic in nature (population) [36]. The treatment of interest was diclofenac combined with TPC by any route of administration (intervention), vs diclofenac monotherapy (control), for pain management. Only the studies that included patients with LBP were considered for qualitative synthesis and meta-analysis considering that this was the focus of this systematic review. A summary of the screening and selection of articles is summarized in Figure 1.

Two independent reviewers assessed each title, summary, and full text (CCO and MNM, when available) based on the selection criteria. Any disagreement was discussed with a third author (CAA) until a consensus was reached.

Extraction of the Data and Assessment of the Risk of Bias

We developed a data extraction format and tested it on five of the studies included. The format was later refined based on the results obtained. We extracted information about the trial setting (country), participants (age, sex), number of patients randomized and studied, number of study arms, experimental treatment (time of administration, duration, and doses), main results, adverse events, and other information (primary author and sponsorship). Two reviewers (CCO and MNM) independently extracted data from each study, assessed the quality of the study methodology using the Cochrane Risk of Bias Tool [35], and any discrepancies were resolved by consensus with a third author (CAA).

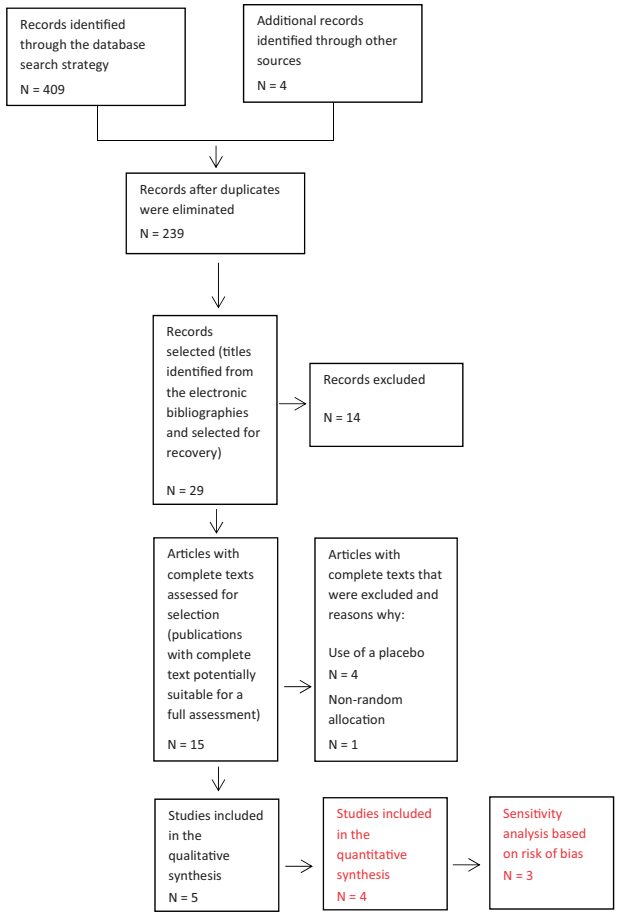

Figure 1. Flowchart describing study selection.

Outcome Measurements

The primary outcome was the proportion of patients who stopped their treatment with diclofenac or diclofenac combined with TPC due to complete pain relief (VAS < 20 mm). The secondary outcomes included decreased pain intensity using validated pain scales (VAS and/or Likert scales) and the occurrence of adverse drug reactions, such as gastrointestinal disorders. Furthermore, we analyzed participant satisfaction, the cost defined by the study authors, and mortality.

Data Synthesis and Analysis

When the measurement of outcomes was sufficiently consistent across trials, we used odds ratios (ORs) for

dichotomous data and mean differences (MDs) for continuous data, with their corresponding 95% confidence intervals (CIs). We included unstandardized MDs because they allow for more direct clinical interpretation. When a study seemed to be missing data, we also contacted the corresponding authors. Using a sensitivity analysis, we explored the effects of including studies with high levels of lost data in our overall assessment of the effect of the treatment. When possible, the denominator for each outcome was based on the initial random allocation, taking into consideration the number of participants based on the group to which they were initially assigned (analysis by intention to treat). We also evaluated clinical heterogeneity (differences between studies in key characteristics of the participants, treatments, or outcome measurements) [37]. The five studies in the systematic review included patients with LBP. Considering that the studies of Vetter, Kuhlwein, Brüggemann, and Mibielli were sufficiently homogeneous in terms of participants, interventions, and outcomes (low clinical heterogeneity), they were included in the meta-analysis. We excluded the study by Levin et al. because it was open label, performed in patients with chronic LBP, used benfotiamine, and the main outcome was reduction in pain intensity and not the number of patients able to stop therapy due to complete pain relief. The methodological heterogeneity is low in our review, as we only evaluated RCTs and most of the studies included in the analysis have a low or indeterminate risk of bias (Figure 2). We considered any value of $I^2 > 50\%$ to be representative of statistically significant heterogeneity between studies. We also carried out a visual inspection of the graphic representation of the study results with 95% CIs to assess heterogeneity.

Rating Evidence Quality

The "Summary of Findings" table shows the primary outcomes from the review, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, version 5.1 (Appendix 2) [35]. We assessed the quality of evidence for each outcome based on the GRADE system for five items: risk of bias, inconsistency, problems with applicability of the evidence, imprecision, and publication bias [33]. Each item was assessed independently by two authors (CCO and MNM), with subsequent discussion to reach consensus, if necessary.

Results

Characteristics of the Studies and Patients

Our search through the electronic databases yielded a total of 409 publications (Figure 1). After reviewing the titles and abstracts (when available) of all the articles, we obtained 15 full-text articles for possible inclusion. Only one of the authors contacted sent the complete study database. After assessing the full texts, we excluded four articles because of nonrandom allocation and one

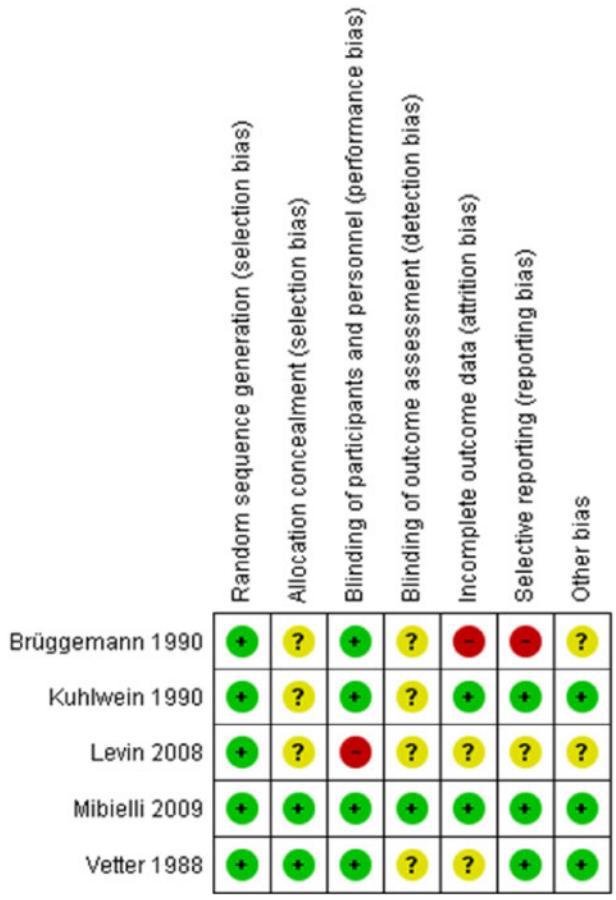

Figure 2. Risk of bias summary in low back pain studies: "+": low risk of bias, "?": unclear risk of bias, "−": high risk of bias.

because of the use of placebo. Five additional articles were excluded because they included patients with conditions other than LBP (i.e., tonsillectomy, lower limb fractures, and osteoarthritis) (Supplementary Data). Finally, we included five articles in the qualitative synthesis. The study selection process is summarized in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart shown in Figure 1.

We included five RCTs in patients with LBP (population; 1,207 participants) comparing the efficacy of diclofenac combined with TPC (intervention) vs diclofenac monotherapy (control) [15,17,32,43]. Only one of the studies [43] used benfotiamine, a fat-soluble derivative of thiamine [44], instead of thiamine. The primary outcome in four of the five studies (the other being the study by Levin et al.) was premature discontinuation of treatment before the study ended due to complete relief of pain.

The trials were published between 1988 and 2009. One of the five trials was financially supported by Merck [16]. The median target sample size was 241.4 (min–max = 38–418) patients. A summary of the five included studies is shown in Table 1.

All the studies had two arms and were double-blind, except for the study by Levin et al. [43], which was open

Table 1. Characteristics of included trials

Study (Reference)	Intervention Regime (Diclofenac + B Vitamins)	Comparator Regime (Diclofenac)	Type of Pain	No.	Primary Outcome	Secondary Outcomes (Reduction in Pain Scores)	Secondary Outcomes (Adverse Events)	Sponsored by the Pharmaceutical Industry
Vetter 1988 [16]	Diclofenac 50 mg/ 8 h orally + thiamine 50 mg, pyridoxine 50 mg, cyanocobalamin 0.25 mg orally for up to 2 weeks	Diclofenac 50 mg/ 8 h orally for up to 2 weeks	Acute low back pain	256	There was a statistically significant difference in the number of patients who stopped treatment on the 7th day due to remission of symptoms (VAS < 2 cm): 19 of 116 in the DB group vs 10 of 122 in the D group ($P < 0.05$).	Percentage reduction in the VAS score: DB (19.9%) vs D group (14.2%) at day 3; DB (40.6%) vs D (28.3%) at day 7; DB (55.1%) vs D (45.5%) at day 14. Reductions in the average VAS score of 14 mm and 10.6 mm on day 3 in the DB vs D, respectively. The authors reported an improvement in the Hoppe Pain Questionnaire score.	There was a greater number of patients who discontinued therapy due to adverse events in the combination therapy group: 9 (7.1%) vs 5 (4.0%; $P > 0.05$). There was no significant difference in the occurrence of gastrointestinal adverse events between the 2 arms of the study.	Yes
Kuhlwein 1990 [15]	Diclofenac 75 mg/d + thiamin 150 mg/d, pyridoxine 150 mg/d, cyanocobalamin 0.75 mg/d orally for up to 7 days	Diclofenac 75 mg/d orally for up to 7 days	Acute low back pain	123	There was a statistically significant difference in the number of patients who stopped treatment on the 3rd day due to remission of symptoms (VAS < 2): 30 of 61 in the DB group vs 15 of 61 in the D group ($P < 0.05$).	Mean reduction in VAS scores on the 3rd day of 42.18 ± 23.5 mm in the DB group vs a reduction of 24.03 ± 18.05 mm in the D group ($P = 0.0001$). Mean reduction in VAS scores at night on day 3 of 28.87 ± 20.8 mm in the DB group vs a reduction of 18.56 ± 15.0 mm in the D group ($P = 0.0006$). Pain relief and mobility of the spine showed statistically significant differences in favor of the DB group.	NR	NR
Brüggemann 1990 [17]	Diclofenac 75 mg/12 h orally + thiamin 150 mg/12 h, pyridoxine 150 mg/12 h, cyanocobalamin 0.75 mg/12 h orally for up to 2 weeks	Diclofenac 75 mg/ 12 h orally for up to 2 weeks	Acute low back pain	418	There was not a statistically significant difference in the number of patients who stopped treatment on the 7th day due to remission of symptoms (VAS < 2 cm): 53 of 184 in the DB group vs 48 of 192 in the D group ($P > 0.05$).	Reduction in pain scores assessed by VAS, but the data were not presented by the authors (reporting bias). Higher improvement of painful symptoms in the DB group (Hoppe Pain Questionnaire) (P values not reported).	No significant differences for gastrointestinal adverse events: 12 of 209 in the combination therapy group vs 7 of 209 in the monotherapy group.	NR

(continued)

Table 1. continued

Study (Reference)	Intervention Regime (Diclofenac + B Vitamins)	Comparator Regime (Diclofenac)	Type of Pain	No.	Primary Outcome	Secondary Outcomes (Reduction in Pain Scores)	Secondary Outcomes (Adverse Events)	Sponsored by the Pharmaceutical Industry
Levin 2008 [43]	Diclofenac 75 mg orally/12 h + benfotiamine 100 mg, pyridoxine 100 mg, cyanocobalamin 0.2 mg orally/12 h	Diclofenac 75 mg orally/12 h	Lumbosacral vertebrogenic radiculopathy	38	Reduction in pain intensity assessed by VAS at days 10 and 24 and at 3 and 6 months of the study. Significant differences between DB vs D were only found at day 24 and were maintained at 3 and 6 months after the start of the study ($P < 0.05$).	Neuropathic Pain Scale and modified Waddell Disability Index. Only DB reduced neuropathic component of pain at day 24th. Similar reductions between both groups were found for the disability index on day 24.	NR	NR
Mibielli 2009 [32]	Diclofenac 50 mg/12 h orally + thiamine 50 mg/12 h, pyridoxine 50 mg/12 h, cyanocobalamin 1 mg/12 h orally for up to 7 days	Diclofenac 50 mg/12 h orally for up to 7 days	Acute low back pain	372	There was a statistically significant difference in the number of patients who stopped treatment on the third day due to remission of symptoms (VAS < 2 cm): 87 of 187 in the DB group vs 55 of 185 in the D group ($P < 0.05$).	Reductions in the VAS of 24.5 ± 18 mm and 20.7 ± 18 mm ($P = 0.044$), in favor of the DB group, on day 3 of the study. Likewise, on day 3 they found a higher percentage of patients with improvement in VAS scores in the DB group (63.1%), compared with the D group (43.8%).	Total number of adverse reactions in the DB group was 46, vs 56 in the D group. Gastrointestinal events: 12 of 187 in the DB group vs 27 of 185 in the D group ($P < 0.05$).	No

D = diclofenac monotherapy; DB = diclofenac plus TPC; LBP = low back pain; NR = not reported; TPC = thiamine, pyridoxine, and cyanocobalamin; VAS = visual analog scale.

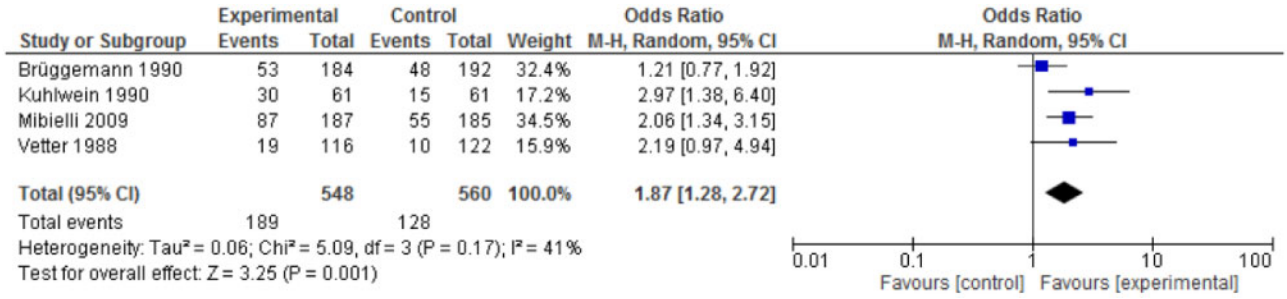

Figure 3. Meta-analysis: early suspension of medication in patients with acute low back pain due to relief of symptoms, including the Brüggemann study. Forest plot of randomized controlled trials examining premature suspension of study medication due to complete pain relief (VAS $\leq$ 2). Study ID is the primary author's last name.

label. The studies conducted in Brazil [32] and Russia [43] were performed at single sites, whereas the three studies conducted in Germany were multicenter [15–17]. Four studies compared the efficacy of diclofenac vs diclofenac in combination with TPC for the management of acute LBP or acute exacerbations of chronic lumbago (1,169 participants), and the Levin study was conducted with patients suffering from chronic LBP. The dose of diclofenac ranged from 25 mg/8 h [15] to 150 mg/d, divided into two or three doses [16,17]. The thiamine and pyridoxine doses ranged from 50 mg/12 h [32] to 150 mg/12 h for each of these compounds [17]. The doses of cyanocobalamin ranged from 0.25 mg/8 h [15,16] to 1 mg/12 h [32]. Two studies included mostly patients with acute lumbago of unspecified origin [17,32], whereas the other three included patients with degenerative lumbar spine disorders [15,16]. All the studies included patients aged 18 and older. The diagnosis or suspicion of herniated disks and other disk disorders was an exclusion criterion in four of the five studies, but not in the Levin study. Other exclusion criteria common to all studies were hypersensitivity to the medications used in the studies, gastric ulcers or recent history of upper digestive tract bleeding, malignant tumors, blood disorders, hepatic and/or renal impairment, current use of anticoagulant therapy, alcohol or drug abuse, pregnancy, or breast feeding [15–17,32].

In two studies, patients had to complete at least three days of treatment [15,32], whereas in the Vetter and Brüggemann study the participants had to take the medication for at least one week [16,17] and in the Levin study patients took the medication for six months, without the possibility to suspend treatment. Secondary outcomes included a decrease in pain intensity assessed with the VAS score (all the studies); patient satisfaction, assessed using the Hoppe Scale [16,17] or subjective evaluations of improvement [15–17,32,43]; the assessment of adverse reactions, including adverse gastrointestinal reactions [16,17,32]; and improvement in functional parameters of the spine, such as the fingers-to-floor distance [32]. Given that the four acute LBP studies had a similar design and reported the same primary outcome (complete pain relief that was sufficient to stop medication before the end of the study), we summarized the data and carried out a meta-analysis for that primary outcome, as well as for the following secondary outcomes: patient satisfaction and the occurrence of gastrointestinal adverse reactions, thereby excluding the Levin study from the meta-analysis.

According to the criteria for judging risk of bias in the Risk of Bias assessment tool [35], the overall risk of bias was low for one of the five (20%) trials, high for two of the five (40%), and unclear for two of the five (40%). In the studies with a high risk of bias, this bias resulted from incomplete outcome data, reporting bias, and performance bias (Figure 2).

Primary Outcome

Enough Pain Relief to Discontinue Therapy Due to Remission of Symptoms

The four studies conducted on patients with acute back pain or acute aggravation of chronic back pain reported a reduction of approximately 50% in the duration of analgesic treatment (from 14 to seven days or seven to three days) as the primary outcome [15–17,32].

We conducted a random-effects meta-analysis (Figure 3) in which a total of 189 of 548 patients achieved the primary outcome in the experimental group (diclofenac plus TPC), vs 128 of 560 patients in the control group (diclofenac monotherapy). This gave the following results, in favor of the combination therapy group: OR = 1.87, 95% CI = 1.28 to 2.72, $P = 0.001$; relative risk (RR) = 1.52, 95% CI = 1.19 to 1.93, $P = 0.0007$; number needed to treat to benefit (NNTB) = 9, 95% CI = 6–16; and risk difference (RD) = 12%, 95% CI = 4% to 20%, $P = 0.003$.

Secondary Outcomes

Reduction in Pain Intensity Documented by VAS

Regarding LBP, all the studies included in this review reported higher pain reduction assessed by VAS in the combination therapy group (diclofenac plus TPC) compared with diclofenac as monotherapy. Levin et al. [43] evaluated this end point as a main outcome. Considering that mean reductions in VAS with their corresponding

standard deviations were only reported in two of the studies [15,32], and one of the studies did not report the mean VAS score [17], it was not possible to carry out a meta-analysis for this outcome (a summary of the secondary outcomes and time points is included in Table 1).

All the studies found a reduction in VAS scores at different points of time (three to 24 days) in favor of the combination therapy group, with statistically significant results in the reports by Kuhlwein, Mibielli, and Levin [15,32,43]. Levin et al. found a difference in favor of the combination treatment group that reached statistical significance on day 24 of the study and was maintained at months 3 and 6 of the assessment [43]. However, this was an open-label study with a high risk of bias (Figure 2).

Occurrence of All Adverse Reactions Associated with Treatment Using Diclofenac Combined with TPC

Regarding the safety profile of the interventions, the following adverse events were reported:

Vetter et al. [16] reported that 18 (14.3%) of the patients in the experimental group had adverse reactions, compared with 19 (15.1%) in the control group. However, nine (7.8%) of the patients in the intervention group had to discontinue therapy due to adverse reactions such as dyspepsia, pyrosis, diarrhea, nausea, vomiting, eructation, diaphoresis, eczema, dizziness, suffocation, chills, and R-R interval prolongation measured with electrocardiogram. However, the authors did not attribute these symptoms exclusively to the use of the study medication. In the control group, five (4.1%) of the patients discontinued treatment due to adverse events. The statistical significance of those results is not presented in the article, but we calculated a nonsignificant OR of 0.93 (95% CI = 0.47 to 1.89).

Mibielli et al. [32] reported the occurrence of adverse reactions in three different periods of the study, as follows: On day 3, 19 patients in the treatment group had adverse reactions, compared with 20 patients in the control group. On day 5 of the study, the frequency was 14 vs 12, and on day 7 it was three vs 12 in the treatment and control groups. In addition, Mibielli et al. [32] reported that three participants in the experimental group were withdrawn from the study due to elevation of transaminases (N = 2) and dyspepsia (N = 1). However, the authors of the study mentioned that all the adverse reactions could be considered typical of treatment with NSAIDs and that, except for the cases mentioned, the laboratory values remained within the reference values for all participants, with no significant differences compared with pretreatment values. For this study, we calculated a nonsignificant OR of 0.75 (95% CI = 0.48 to 1.19).

Brüggemann et al. [17] reported that 70 patients in the study had adverse drug reactions, but the distribution between the study arms was not reported. Considering that only two studies reported this outcome, we did not perform a meta-analysis for total adverse events.

Participants' Tolerance, Including the Incidence of Gastrointestinal Disorders

Three studies contained specific information about gastrointestinal adverse reactions [16,17,32].

Vetter et al. [16] reported that 14 patients in the treatment group and 13 patients in the control group had gastrointestinal adverse reactions, including dyspepsia, nausea, vomiting, constipation, diarrhea, eructation, pyrosis, meteorism, and abdominal distension (OR = 1.15, 95% CI = 0.52 to 2.57).

Brüggemann et al. [17] reported that 12 (5.7%) patients in the combination therapy group and seven (3.3%) patients in the control group had gastrointestinal disorders that led them to withdraw from the study; however, *P* values were not reported. We calculated a nonsignificant OR of 1.76 (95% CI = 0.68 to 4.56). In addition, this study reported two cases of temporary elevation of serum glutamic oxaloacetic transaminase (SGOT) but did not specify which study arm the patients with this adverse reaction belonged to.

Mibielli et al. [32] reported 12 gastrointestinal adverse reactions including dyspepsia, flatulence, nocturnal pyrosis, diarrhea, and constipation in the experimental group, compared with 27 gastrointestinal reactions in the control group (OR = 0.40, 95% CI = 0.20 to 0.82).

A meta-analysis for this outcome did not find significant differences between the two groups (OR = 0.90, 95% CI = 0.37 to 2.17, $P = 0.81$) (Figure 4).

Participant Satisfaction Defined by the Authors of the Study

In all five studies, patient satisfaction was assessed using qualitative scales [15–17,32,43].

Vetter et al. [16] used a qualitative scale based on the following items: "better," "no change," "worse," "no information available." Brüggemann et al. [17] and Kuhlwein et al. [15] used a similar qualitative scale: "very good," "good," "no change," and "poor" in relation to the patients' general perception after therapy.

For this purpose, Mibielli et al. [32] used a subjective evaluation (satisfied vs unsatisfied) in patients with LBP. After checking the database of this study, at visit 2 (after three days) 162 patients out of 187 reported satisfaction in the combination therapy group vs 152 out of 185 in the monotherapy group. At visit 3 (after five days) 85 patients out of 87 reported satisfaction in the combination therapy group vs 115 out of 120 in the monotherapy group. At visit 4 (after seven days), 16 patients out of 16 reported satisfaction in the combination therapy group vs 67 out of 68 in the monotherapy group ($P > 0.05$).

By setting cutoff points between patients who reported some grade of improvement and those who did not at their last visit in the study, we made this variable

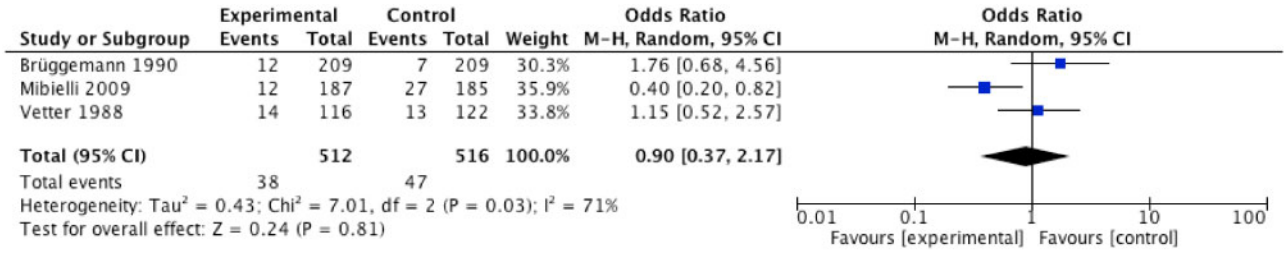

Figure 4. Meta-analysis: gastrointestinal adverse events. Forest plot of randomized controlled trials examining the occurrence of gastrointestinal adverse events.

dichotomous, enabling the corresponding meta-analysis of patients with acute back pain, which did not find significant differences between the two groups (OR = 1.48, 95% CI = 0.76–2.87, $P = 0.24$) (Figure 5).

Levin et al. [43] reported substantial or moderate improvement on the Neuropathic Pain Scale in 66% of the patients who received the combination therapy, compared with 34% of the patients given only diclofenac.

Cost Defined by the Authors of the Study

This outcome was not discussed in any of the studies included in this review.

Mortality

No deaths were reported in any of the studies included in this review.

Sensitivity Analysis Based on Risk of Bias

As part of the sensitivity analysis, when we excluded the Brüggemann et al. study [17], which was considered to have a high risk of bias (attrition and reporting biases), the following results were found in favor of the experimental group: OR = 2.23, 95% CI = 1.59 to 3.13, $P < 0.00001$; RR = 1.68, 95% CI = 1.34 to 2.11, $P < 0.00001$; NNTB = 6, 95% CI = 5 to 11; RD = 15%, 95% CI = 6% to 24%, $P = 0.001$ (Figure 6).

Discussion

This systematic review summarizes the available evidence regarding the combination of TPC with diclofenac for LBP. It is based on moderate- and high-quality evidence, which revealed a reduction in treatment duration of approximately 50% in patients with acute LBP who received combination therapy. Thus, we propose that the addition of these vitamins could work as a useful analgesic adjuvant for managing patients with acute back pain. The combination of TPC with diclofenac has shown contradictory or inconclusive results in postoperative pain, for both tonsillectomy [38,39] and lower limb fractures (a summary of these studies is included in the Supplementary Data) [40,41]. Although combination therapy may be more effective than diclofenac in monotherapy for treating conditions such as osteoarthritis [42] and lower limb fractures [41], the current evidence is insufficient to recommend it as a firstline therapy.

Strengths and Weaknesses of our Methodology

Our study had several strengths that should be considered. First, we conducted a rigorous and extensive review of the literature, including searches of records of clinical studies, and we contacted the authors of the studies published. Second, by collecting a large amount of information, we were able to achieve the necessary amount of information to analyze the effect of adding TPC to diclofenac for managing LBP. Third, our systematic review was associated with a rating of the quality of evidence, thus providing transparency in our presentation of the available evidence and the degree to which we can state that our estimates of the effect are accurate. The main weakness of our review was the relatively small number of studies examining pain conditions other than acute back pain, making it difficult to establish the benefits of this treatment for other pathologies.

Reduction of the Duration of Analgesic Therapy to Half the Usual Time in Patients with Acute Back Pain and Safety of the Intervention

The results of the meta-analysis in patients with LBP revealed that combination treatment using diclofenac plus TPC reduces the time of exposure to NSAIDs, compared with diclofenac monotherapy. The number needed to treat to achieve this benefit is only six ($P = 0.001$). This is also significant from a clinical point of view, considering that the cumulative dose of diclofenac could be reduced by approximately 50%. In the meta-analysis, we did not find significant differences in total or gastrointestinal adverse reactions. In general, it is well accepted that B vitamins have a favourable safety profile [45]. We hypothesize that the absence of thiamine toxicity may be related to reduced body accumulation, considering that it is a water-soluble vitamin and is quickly eliminated renally [46]. In the case of pyridoxine, isolated cases of peripheral neuropathy, dermatitis, photosensitivity, dizziness, and nausea have been reported with administration of long-term doses higher than 1 g/d (five times the usual dose) [47]. Anaphylactic shock after parenteral administration of cyanocobalamin has been reported in isolated cases [48]. Intervention trials indicate that vitamin B12 by oral route

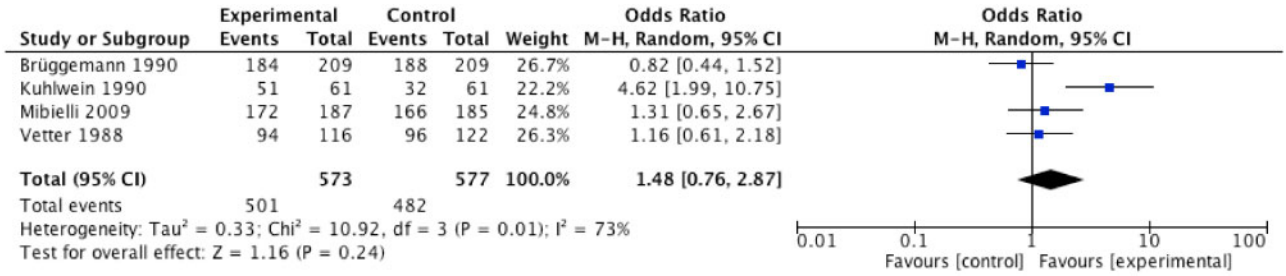

Figure 5. Meta-analysis: patient satisfaction Forest plot of randomized controlled trials examining patient satisfaction according to the number of patients who reported some grade of improvement and those who did not at their last visit in the study.

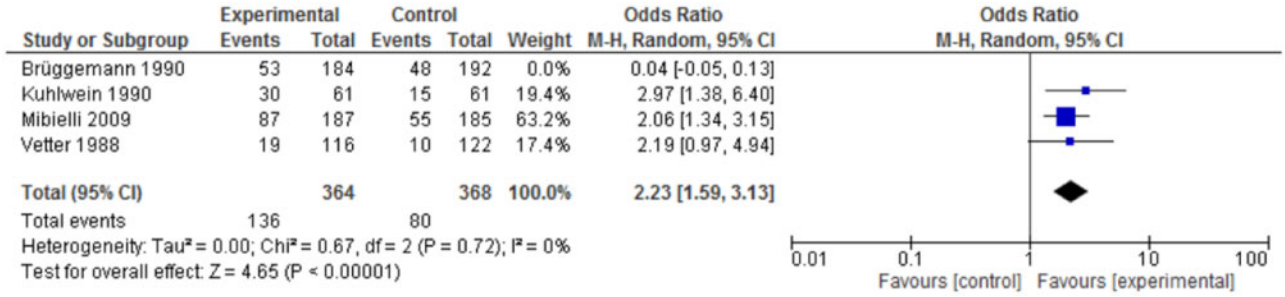

Figure 6. Meta-analysis: early suspension of medication in patients with acute low back pain due to relief of symptoms, without including the Brüggemann study. Forest plot of randomized controlled trials examining premature suspension of study medication due to complete pain relief (VAS $\leq$ 2), without including the Brüggemann study (sensitivity analysis). Study ID is the primary author's last name.

has low potential for toxicity: in the NORVIT [49] and HOPE 2[45] trials, vitamin B12 supplementation (in combination with folic acid and vitamin B6) did not cause any serious adverse events at doses of 0.4 mg for 40 months (NORVIT trial) and 1.0 mg for five years (HOPE 2 trial).

First Quantitative Analysis of the Effect of Combining B Vitamins (TPC) with Diclofenac for LBP Management

This is the first meta-analysis of the effect of adding TPC to diclofenac during analgesic therapy in patients with acute LBP.

The results of this review partly coincide with those of another systematic review by Roelofs et al. performed on patients with back pain [31]. That review, conducted using Cochrane's methodology, did not include the study by Mibielli et al. [32], because that was published the following year. However, it included studies by Vetter et al. [16], Kuhlwein et al. [15], and Brüggemann et al. [17], and the first two were considered to be of high quality by the authors of the review. Because of the conflicting results and lack of significant differences in the Brüggemann et al. [17] study, Roelofs and collaborators deemed the evidence to be contradictory and possibly insufficient to demonstrate higher analgesic efficacy of the combination therapy over diclofenac monotherapy in patients with acute back pain. In addition, with only two high-quality studies, the evidence available at that time was insufficient to perform a meta-analysis.

Therefore, we included Mibielli et al. [32] in the current random-effects meta-analysis with a total of >1,000 patients (N = 1,108) with acute back pain. Including this study revealed that adding TPC to the standard therapy with diclofenac shortened the duration of treatment to half the usual time.

Two reports in post-tonsillectomy patients [38,39] who received combination therapy found a reduction in the dose of diclofenac as a secondary outcome, reporting an average reduction in the dose of diclofenac of approximately 50 mg/d per patient ($P < 0.00001$). However, as these clinical trials have several methodological weaknesses (i.e., they did not report the use of rescue doses with morphine between the two study groups and incomplete outcome data, among others), we consider that both reports had high risk of bias (Supplementary Data).

Most of the studies included in this systematic review reported a reduction in pain scores assessed by VAS and Likert scale, in favor of the combination therapy group (Table 1; Supplementary Data). The greatest reduction in VAS scores was found in two studies in patients with lower limb fractures and severe osteoarthritis [41,42], with an additional reduction of almost two points on the VAS scale, compared with patients who received only diclofenac.

In patients with severe osteoarthritis of the knee and lumbosacral radiculopathy, higher satisfaction was reported using qualitative scales in the combination therapy group compared with those given diclofenac monotherapy [42,43]. However, in our meta-analysis, we did not find significant differences in LBP. Considering that the

heterogeneity of this meta-analysis was higher than 50% ($I^2 = 73\%$), this result must be interpreted with caution. This lack of difference could be explained by the fact that acute LBP is usually a self-limited condition, and in half of the reports, the satisfaction was evaluated after 14 days [16,17]. Only the studies that evaluated this outcome in the early phase of the condition (after three days and seven days) reported higher levels of satisfaction [15,32].

Exhaustiveness and Applicability of the Evidence

Considering that Brüggemann et al. [17] was classified as having high risk of bias, we carried out a sensitivity analysis excluding this study in the meta-analysis for the primary outcome in patients with LBP. We found a higher OR for this outcome (OR = 2.23, 95% CI = 1.59–3.13) (Figure 6).

In terms of overall therapy for back pain management, none of the studies mentioned self-care or psychotherapy, or the use of alternative medicine or supplementary forms of treatment (e.g., acupuncture, osteopathy). Physical therapy was permitted in Vetter et al. [16], but neither the number of sessions nor the type of session involved in each of the study arms was reported. However, this type of treatment was not allowed in the studies by Kuhlwein et al. [15] or Mibielli et al. [32] during the first three days of the study. Brüggemann et al. [17] did not mention the use of this therapy. The concomitant use of analgesics other than those assessed was not allowed in any of the four acute LBP studies included in the meta-analysis [15–17,32] and was considered by the investigators an exclusion criterion.

Clinical Implications

The current review and meta-analysis revealed evidence confirming a superior analgesic effect for the combination of diclofenac with TPC over conventional therapy (diclofenac monotherapy) in patients with acute LBP, or acute exacerbations of the chronic condition, with or without degenerative lumbar spine disease without discopathy. The doses of diclofenac ranged between 75 and 150 mg/d, whereas the doses of vitamins B1 and B6 were between 100 and 300 mg/d. The dose of vitamin B12 ranged between 0.75 [15,16] and 2 mg/d in the study by Mibielli et al. [32], which reported the greatest levels of pain relief. These results are in agreement with those reported by the Magaña-Villa et al. [42] study of patients with severe osteoarthritis of the knee and the Ponce-Monter et al. [41] study of patients with lower limb fractures and surgery, in which cyanocobalamin doses of 2 mg/d or more were used. Importantly, cyanocobalamin as monotherapy delivered by intramuscular route has previously been assessed in patients with chronic back pain against placebo [50] in an RCT, with a greater reduction in the VAS in patients who received vitamin B12 (average reduction of 66 points), compared with those given placebo (average reduction of 34 points; $P < 0.0001$). We speculate that the analgesic effect of combining thiamine, pyridoxine, and cyanocobalamin may be largely due to vitamin B12.

Two additional pilot studies suggested a benefit of the addition of TPC to diclofenac for acute LBP management and spinal degenerative rheumatic diseases [51,52]. However, these studies had multiple risks of bias including selective reporting bias, as well as selection, performance, detection, and attrition bias, among others; for this reason, they were not included in the qualitative synthesis or in the present meta-analysis.

The synergistic effect of combining diclofenac with TPC enables patients to resume work activities sooner and may reduce the economic burden of disease associated with LBP, considering that this is the most disabling condition worldwide. In addition, combination therapy was associated with lower pain intensity and greater patient satisfaction at an early stage of the disease, with fewer gastrointestinal adverse reactions, probably due to a reduction in cumulative doses of diclofenac.

As we mentioned before, the antinociceptive action of B vitamins (B1, B6, and B12) is explained by several mechanisms of action complementary to those of NSAIDs. Therefore, these vitamins, in combination with diclofenac (and possibly other NSAIDs) can be useful for the management of painful conditions that present with inflammatory and neuropathic components at the same time, known as mixed pain syndromes (e.g., LBP) [53]. Correspondingly, in a recent prospective study (N = 411), the effectiveness of the TPC combination in peripheral neuropathy was evaluated, and it was found that fixed doses of this combination generate a significant reduction in pain intensity, according to the VAS scale [54].

Conclusions

The available data included in this systematic review and meta-analysis support, with moderate–high evidence, a greater efficacy of diclofenac in combination with TPC compared with diclofenac as monotherapy for the management of acute LBP, with the most significant effect being the reduction in treatment duration.

To confirm the efficacy and safety of this intervention, future clinical studies should include TPC as a new analgesic adjuvant therapy in several types of pain, including mixed pain syndromes, such as LBP, osteoarthritis, postoperative pain, and cancer, among others. In addition, it may be valuable to investigate whether the use of TPC as an analgesic adjuvant in patients with chronic pain helps to reduce the necessary daily doses of NSAIDs and other analgesics (i.e., opioids or antiepileptic drugs such as pregabalin), along with the incidence of adverse reactions.

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Supplementary Data

Supplementary Data may be found online at http://painmedicine.oxfordjournals.org.

References

1. Hoy D, Bain C, Williams G, et al. A systematic review of the global prevalence of low back pain. Arthritis Rheum 2012;64(6):2028–37.
2. Manchikanti L, Singh V, Falco FJE, Benyamin RM, Hirsch JA. Epidemiology of low back pain in adults. Neuromodulation 2014;17(Suppl 2):3–10.
3. Deyo RA, Dworkin SF, Amtmann D, et al. Report of the NIH Task Force on Research Standards for Chronic Low Back Pain. Int J Ther Massage Bodywork 2015;8(3):16–33.
4. Trask C, Bath B, Johnson PW, Teschke K. Risk factors for low back disorders in Saskatchewan farmers: Field-based exposure assessment to build a foundation for epidemiological studies. JMIR Res Protoc 2016;5(2):e111.
5. Deyo RA, Mirza SK, Martin BI. Back pain prevalence and visit rates: Estimates from U.S. national surveys, 2002. Spine 2006;31(23):2724–7.
6. Hoy D, Brooks P, Blyth F, Buchbinder R. The epidemiology of low back pain. Best Pract Res Clin Rheumatol 2010;24(6):769–81.
7. Sanzarello I, Merlini L, Rosa MA, et al. Central sensitization in chronic low back pain: A narrative review. J Back Musculoskelet Rehabil 2016;29(4):625–33.
8. Beneck GJ, Kulig K. Multifidus atrophy is localized and bilateral in active persons with chronic unilateral low back pain. Arch Phys Med Rehabil 2012;93(2):300–6.
9. van Roy P, Barbaix E, Clarijs JP, Mense S. Anatomical background of low back pain: variability and degeneration of the lumbar spinal canal and intervertebral disc. Schmerz. 2001;15(6):418–24.
10. Vos T, Allen C, Arora M, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1545–602.
11. Golob AL, Wipf JE. Low back pain. Med Clin North Am 2014;98(3):405–28.
12. Lussier D, Huskey AG, Portenoy RK. Adjuvant analgesics in cancer pain management. Oncologist 2004;9(5):571–91.
13. Baldini A, Von Korff M, Lin EHB. A review of potential adverse effects of long-term opioid therapy: A practitioner's guide. Prim Care Companion CNS Disord 2012;14(3):PCC.11m01326.
14. Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: A clinical practice guideline from the American College of Physicians. Ann Intern Med 2017;166(7):514–30.
15. Kuhlwein A, Meyer HJ, Koehler CO. Reduced diclofenac administration by B vitamins: Results of a randomized double-blind study with reduced daily doses of diclofenac (75 mg diclofenac versus 75 mg diclofenac plus B vitamins) in acute lumbar vertebral syndromes. Klin Wochenschr 1990;68(2):107–15.
16. Vetter G, Brüggemann G, Lettko M, et al. Shortening diclofenac therapy by B vitamins. Results of a randomized double-blind study, diclofenac 50 mg versus diclofenac 50 mg plus B vitamins, in painful spinal diseases with degenerative changes. Z Rheumatol 1988;47(5):351–62.
17. Brüggemann G, Koehler CO, Koch EM. Results of a double-blind study of diclofenac + vitamin B1, B6, B12 versus diclofenac in patients with acute pain of the lumbar vertebrae. A multicenter study. Klin Wochenschr 1990;68(2):116–20.
18. Hurt JK, Coleman JL, Fitzpatrick BJ, et al. Prostatic acid phosphatase is required for the antinociceptive effects of thiamine and benfotiamine. PLoS One 2012;7(10):e48562.
19. Song X-S, Huang Z-J, Song X-J. Thiamine suppresses thermal hyperalgesia, inhibits hyperexcitability, and lessens alterations of sodium currents in injured, dorsal root ganglion neurons in rats. Anesthesiology 2009;110(2):387–400.
20. Thériault O, Poulin H, Thomas GR, Friesen AD, Al-Shaqha WA, Chahine M. Pyridoxal-5'-phosphate (MC-1), a vitamin B6 derivative, inhibits expressed P2X receptors. Can J Physiol Pharmacol 2014;92(3):189–96.
21. Chiang E-P, Smith DE, Selhub J, Dallal G, Wang Y-C, Roubenoff R. Inflammation causes tissue-specific depletion of vitamin B6. Arthritis Res Ther 2005;7(6):R1254–62.
22. Erfanparast A, Tamaddonfard E. Effects of intracortical microinjection of vitamin B12 on penicillin-induced epileptiform activity in rats. Acta Neurobiol Exp (Wars) 2015;75(2):200–7.
23. Hosseinzadeh H, Moallem SA, Moshiri M, Sarnavazi MS, Etemad L. Anti-nociceptive and anti-inflammatory effects of cyanocobalamin (vitamin B12) against acute and chronic pain and inflammation in mice. Arzneimittelforschung 2012;62(7):324–9.
24. Moallem SA, Hosseinzadeh H, Farahi S. A study of acute and chronic anti-nociceptive and anti-inflammatory effects of thiamine in mice. Iran Biomed J 2008;12(3):173–8.
25. McCarty MF. High-dose pyridoxine as an "anti-stress" strategy. Med Hypotheses 2000;54(5):803–7.
26. Lerner V, Miodownik C, Kaptsan A, et al. Vitamin B6 treatment for tardive dyskinesia: A randomized,

double-blind, placebo-controlled, crossover study. J Clin Psychiatry 2007;68(11):1648–54.
27. Friso S, Jacques PF, Wilson PW, Rosenberg IH, Selhub J. Low circulating vitamin B(6) is associated with elevation of the inflammation marker C-reactive protein independently of plasma homocysteine levels. Circulation 2001;103(23):2788–91.
28. Deng X-T, Han Y, Liu W-T, Song X-J. B Vitamins potentiate acute morphine antinociception and attenuate the development of tolerance to chronic morphine in mice. Pain Med 2017;18(10):1961–74.
29. Menezes RR, Godin AM, Rodrigues FF, et al. Thiamine and riboflavin inhibit production of cytokines and increase the anti-inflammatory activity of a corticosteroid in a chronic model of inflammation induced by complete Freund's adjuvant. Pharmacol Rep 2017;69(5):1036–43.
30. Onk D, Mammadov R, Suleyman B, et al. The effect of thiamine and its metabolites on peripheral neuropathic pain induced by cisplatin in rats. Exp Anim 2018;67(2):259–69.
31. Roelofs P, Deyo RA, Koes BW, Scholten R, van Tulder MW. Non-steroidal anti-inflammatory drugs for low back pain. Cochrane Database Syst Rev 2008;1:CD000396.
32. Mibielli M, Geller M, Cohen J, et al. Diclofenac plus B vitamins versus diclofenac monotherapy in lumbago: The DOLOR study. Curr Med Res Opin 2009; 25(11):2589–99.
33. GRADE Handbook. 2019. https://gdt.gradepro.org/app/handbook/handbook.html (accessed March 5, 2019).
34. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. PLoS Med 2009;6(7):e1000097.
35. Cochrane Handbook for Systematic Reviews of Interventions. 2018. https://handbook-5-1.cochrane.org/ (accessed December 6, 2018).
36. Kosek E, Cohen M, Baron R, et al. Do we need a third mechanistic descriptor for chronic pain states? Pain 2016;157(7):1382–6.
37. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Matthias Egger, George Davey Smith, Douglas G Altman, eds. Systematic Reviews in Health Care. New York: John Wiley & Sons, Ltd; 2008:285–312.
38. Medina-Santillán R, Pérez-Flores E, Mateos-García E, Reyes-García G, Granados-Soto V, Flores-Murrieta FJ. AB-vitamin mixture reduces the requirements of diclofenac after tonsillectomy: A double-blind study. Drug Dev Res 2005;66(1):36–9.
39. Pérez-Flores E, Medina-Santillán R, Reyes-García G, Mateos-García E. Combination of diclofenac plus B vitamins in acute pain after tonsillectomy: A pilot study. Proc West Pharmacol Soc 2003;46:88–90.
40. Garza AF, Monroy-Maya R, Soto-Ríos M, et al. A pilot study of the effect of diclofenac with B vitamins for the treatment of acute pain following lower-limb fracture and surgery. Proc West Pharmacol Soc 2008; 51:70–2.
41. Ponce-Monter HA, Ortiz MI, Garza-Hernández AF, et al. Effect of diclofenac with B vitamins on the treatment of acute pain originated by lower-limb fracture and surgery. Pain Res Treat 2012;2012:1–5.
42. Magaña-Villa MC, Rocha-González HI, Fernández del Valle-Laisequilla C, et al. B-vitamin mixture improves the analgesic effect of diclofenac in patients with osteoarthritis: A double blind study. Drug Res (Stuttg) 2013;63(6):289–92.
43. Levin O, Moseĭkin I. Vitamin B complex (milgamma) in the treatment of vertebrogenic lumbosacral radiculopathy. Zh Nevrol Psikhiatr Im S S Korsakova 2009;109(10):30–5.
44. Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic polyneuropathy: A three-week randomized, controlled pilot study (BEDIP study). Int J Clin Pharmacol Ther 2005;43(2):71–7.
45. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med 2006;354(15):1567–77.
46. Smithline HA, Donnino M, Greenblatt DJ. Pharmacokinetics of high-dose oral thiamine hydrochloride in healthy subjects. BMC Clin Pharmacol 2012;12(1):1–10.
47. Hughes R. Investigation of peripheral neuropathy. BMJ 2010;341:1161–62.
48. Wajih Ullah M, Amray A, Qaseem A, Siddiqui T, Naeem T. Anaphylactic reaction to cyanocobalamin: A case report. Cureus 2018;10(5):e2582.
49. Bønaa KH, Njølstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006; 354(15):1578–88.
50. Mauro GL, Martorana U, Cataldo P, Brancato G, Letizia G. Vitamin B∼1∼2 in low back pain: A randomised, double-blind, placebo-controlled study. Eur Rev Med Pharmacol Sci 2000;4:53–8.
51. Lettko M, Bartoszyk GD. Reduced need for diclofenac with concomitant administration of pyridoxine and other B vitamins. Ann NY Acad Sci 1990;585:510–2.
52. Khan TA, Ahmad A, Haider IZ. Low dose diclofenac sodium with vitamin-B complex compared with diclofenac alone. Professional Med J 2008;15:440–4.
53. Freynhagen R, Arevalo Parada H, Calderon-Ospina CA, et al. Current understanding of the mixed pain concept: A brief narrative review. Curr Med Res Opin. 2019;35(6):1011–18.
54. Hakim M, Kurniani N, Pinzon RT, et al. Management of peripheral neuropathy symptoms with a fixed dose combination of high-dose vitamin B1, B6 and B12: A 12-week prospective non-interventional study in Indonesia. Asian J Med Sci. 2018;9(1):32–40.

Appendix 1. Search equation in PUBMED

The following search strategy was developed for PUBMED and was adapted for the other databases to be searched

1. randomized controlled trial[Publication Type]
2. controlled clinical trial[Publication Type]
3. randomized[Title/Abstract]
4. diclofenac[Title/Abstract]
5. drug therapy[sh]
6. clinical trials as topic[sh]
7. randomly[Title/Abstract]
8. trial [Title/Abstract]
9. groups[Title/Abstract]
10. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
11. Animals[mh] not (humans)[mh]
12. 10 not 11
13. pain[sh]
14. Thiamine
15. Vitamin B1
16. Pyridoxine
17. Vitamin B6
18. Cyanocobalamin
19. Vitamin B12
20. Vitamin B Complex
21. Neurobion
22. 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21
23. 12 and 13 and 22

Appendix 2. Diclofenac compared with diclofenac + B-complex vitamins for the management of acute back pain

Study group: patients aged >18 with acute back pain (for >3 days), without related disk pathology
Scope: outpatient care
Intervention: fixed-dose combination of diclofenac + thiamine + pyridoxine + cyanocobalamin taken orally
Comparison factor: oral diclofenac

	Examples of Comparative Risks					
	Assumed Risk	Corresponding Risk				
Outcomes	Diclofenac	Diclofenac + B Vitamins	Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
Sufficient pain relief to discontinue therapy due to remission of symptoms	80 out of 368 participants achieved the primary outcome	136 out of 364 participants achieved the primary outcome	OR 2.23 (1.59 to 3.13) RR 1.68 (1.34 to 2.11) RD 0.15 (0.06 to 0.24)	732 participants (3 studies)	High	A statistically significant difference was found for the primary outcome (early discontinuation of therapy due to resolution of symptoms) in three studies with good methodological quality and low risk bias.
Reduction of pain intensity in patients with acute back pain	Kuhlwein 1990: 24.03-mm reduction on the VAS Mibielli 2009 20.7-mm reduction on the VAS	Kuhlwein 1990: 42.18-mm reduction on the VAS Mibielli 2009: 24.5-mm reduction on the VAS	MD 10.59 (–3.45 to 24.64)	494 participants (2 studies)	Moderate	A trend toward greater reduction in the pain scores assessed by VAS was found in patients with acute back pain in the participants in the intervention group: Larger sample sizes may be required to demonstrate statistical significance. The studies included in this meta-analysis were of good quality methodologically and low risk bias. High heterogeneity and a wide confidence interval for pain reduction outcome were found.
Satisfaction of the patients with acute back pain	441 out of 560 participants achieved this secondary outcome	477 out of 548 participants achieved this secondary outcome	OR 1.48 (0.76 to 2.97) RR 1.06 (0.95 to 1.19) RD 0.06 (–0.03 to 0.16)	1,150 participants (4 studies)	Moderate	No statistically significant difference was found in the number of patients who reported some degree of subjective improvement (satisfaction) in the control group compared with the intervention group. Three of the four studies included in this meta-analysis were of good quality in terms of methodology. The Brüggemann study had reporting and attrition bias due to incomplete outcome data. For that reason, the Brüggemann report was considered a low-quality study.

(continued)

Appendix 2. continued

Study group: patients aged >18 with acute back pain (for >3 days), without related disk pathology
Scope: outpatient care
Intervention: fixed-dose combination of diclofenac + thiamine + pyridoxine + cyanocobalamin taken orally
Comparison factor: oral diclofenac

	Examples of Comparative Risks					
	Assumed Risk	Corresponding Risk				
Outcomes	Diclofenac	Diclofenac + B Vitamins	Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
Total adverse reactions in patients with acute back pain	75 out of 236 patients had this secondary outcome	64 out of 249 participants had this secondary outcome	OR 0.81 (0.55 to 1.18) RR 0.85 (0.63 to 1.14) RD –3.67 (–10.19 to 2.86)	624 participants (2 studies)	High	No statistically significant difference was found between the frequencies of total adverse reactions in the control group compared with the intervention group. The two studies included in this meta-analysis were of good quality in terms of methodology with low heterogeneity.
Gastrointestinal adverse events	47 out of 516 patients had this secondary outcome	38 out of 512 participants had this secondary outcome	OR 0.90 (0.37 to 2.17) RR 0.91 (0.41 to 2.03) RD –0.01 (–0.09 to 0.06)	1,028 participants (3 studies)	Moderate	No statistically significant difference was found in the number of patients who reported gastrointestinal adverse events in the control group compared with the intervention group. Two of the three studies included in this meta-analysis were of good quality in terms of methodology. The Brüggemann study had reporting and attrition bias due to incomplete outcome data. For that reason, the Brüggemann report was considered a low-quality study.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

CI = confidence interval; MD = mean difference; OR = odds ratio; RD = risk difference; RR = risk ratio; VAS = visual analog scale.