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REVIEW

WILEY

Efficacy of topical versus oral analgesic medication compared to a placebo in injured athletes: A systematic review with meta-analysis

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Abstract

Background: Athletes are injured frequently and often take analgesic medication. Moreover, athletes commonly use non-prescription topical and oral medications with little guidance. Despite wide use, relatively few studies exist on the efficacy of pain medication in injured athletes compared to a placebo.

Objective: To determine efficacy of topical or oral medications in pain reduction compared to a placebo in injured athletes.

Study Design: A systematic review and meta-analysis.

Methods: We conducted an electronic search using Medline/Pubmed, Web of Science, Ovid, and SportDiscus for all literature relating to topical or oral medications in athletes for pain management post-injury. Two reviewers screened the studies and measured their quality. To determine efficacy, we calculated the Hedges' g value.

We created forest plots with 95% CI to graphically summarize the meta-analyses.

Results: There was a significant pooled effect size reflecting a reduction in pain outcomes for the topical treatment versus placebo ($g = -0.64$; 95% CI [−0.89, −0.39]; $p < 0.001$). There was not a significant reduction in pain outcomes for the oral treatment versus placebo ($g = -0.26$; 95% CI [−0.60, 0.17]; $p = 0.272$).

Conclusion: Topical medications were significantly better at reducing pain compared to oral medications versus a placebo in injured athletes. These results are different when compared to other studies that used experimentally induced pain versus musculoskeletal injuries. The results from our study suggest that athletes should use topical medications for pain reduction, as it is more effective, and there are less reported adverse effects compared to oral medication.

KEYWORDS

drug, game, inflammation, injury, muscle, NSAID, pain, sport

1 | INTRODUCTION

Elite athletes are defined as competing in a sport at a high level for their age category.[1] There is a high prevalence of sports injuries among elite athletes.[2] Sport injuries can be acute or chronic and are often associated with pain.[2] Though there can be dangers in masking pain when an injury is not fully healed, athletes need to find ways to rapidly manage their pain to be able to return to play quickly. Regardless of pain tolerance, most athletes will typically seek pain management, often including but not limited to analgesic medications.[3–6] Athletes frequently use analgesic medications early on in the management of an injury as they are available over-the-counter (OTC), and do not require a prescription.[7] One study indicated that 46% of National Collegiate Athletic Association (NCAA) female athletes and 38% of NCAA male athletes who were experiencing injury-related pain were taking non-steroidal anti-inflammatory drugs (NSAIDs).[8] Among them, 70% of female athletes had purchased the NSAIDs themselves, versus 61% of male athletes, suggesting that they might not be part of their medical record or known by the medical staff. Another study reported that 62% of collegiate athletes use non-prescription drugs for injury-related pain management.[3] Many of these athletes do not consult healthcare practitioners prior to self-medicating and are unaware of the potential adverse effects associated with medication use.[7] They are also not properly informed on which medication can be the best for their injury management. While many athletes will use analgesic medications specifically for sustained injuries, it is also reported that several athletes use them prophylactically before competition.[9] There are relatively few studies done on the use of analgesics drugs in injured athletes for pain management.

Athletes experience pain differently than non-athletes, often showing a higher pain tolerance than non-athletes.[10,11] It is unclear whether athletes would respond to analgesic medications the same way a non-athlete would, considering the differences in their pain tolerance.[12] Previous studies on the efficacy of pain medications in athletes have been completed using various experimentally induced pain models including delayed onset muscle soreness (DOMS). Experimentally induced pain may not have the same inflammation cascade or psychological impact as an actual musculoskeletal injury.[13,14] In fact, experimental models inducing pain or DOMS are done to control for psychological factors that are present post-injury (Petersen-Felix & Arendt-Nielsen, 2002). While some suggest the inflammation response is similar in DOMS, the mechanism of DOMS is still unknown.[14] In addition, the recovery after DOMS is more defined compared to an actual injury.[15,16] The psychological response will be different when comparing DOMS to an injury and this will also contribute to a wider experience of pain.[13,14] During a musculoskeletal injury, the symptomology begins at the time of the mechanism or during continued exercise.[14] In DOMS, the symptomology begins 6–12 h post-exercise and increases to reach a maximum pain level at 48–72 h.[14] It is thus difficult to say if a medication response to DOMS would be the same as a medication response to a musculoskeletal injury.[14]

The placebo effect makes evaluating pain treatment challenging.[17] Studies aiming to show if a drug is effective at reducing pain will often include a placebo group,[17] and are in some instances required to do so.[18] Many of these studies are done on non-athletes. Knowing that athletes experience pain differently than non-athletes, displaying a higher pain tolerance,[12] one may question whether athletes also feel placebo analgesia differently than non-athletes. One study concluded that athletes experience the placebo effect less compared to non-athletes when provoked with painful stimulation.[10] It is unclear whether this finding translates to sport-related injuries as well, and if there would be a difference depending on medication used or type of injury. The purpose of this review is to compare the pain reduction in athletes treating musculoskeletal injuries with topical or oral over-the-counter medications versus placebo medications. There are previous reviews published comparing medications to placebo in the non-athlete population, but it is unclear is the results would be different in athletes. Knowing this information can help healthcare practitioners make suggestions that would help an athlete to better manage their pain. Furthermore, there are less reported adverse effects with the use of topical medications compared to oral counterparts, and as such we would want to know if these medications are of equal effectiveness in athletes.[19] If they are, then topical medications would be the safer choice.

2 | METHODS

2.1 | Data sources and search strategy

We used the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines to conduct and report this study.[20] We searched four electronic databases: Web of Science, Ovid/Medline, PubMed/NCBI, and SPORTDiscus from their inception to February 2022. Our search strategy was based on a combination of key terms, synonyms, Boolean conjunction, and truncation (Appendix 1). Two reviewers independently screened titles and abstracts of potential articles in the initial search. In case of disagreement, a third reviewer, who is an expert in pain research, helped to decide if a study could be included. Following this, the two reviewers screened full

texts for eligibility. We also performed hand-searching of references and times-cited lists of included articles and authors' bibliographies to find relevant articles not identified using the predefined search strategy (Figure 1).

2.2 | Inclusion and exclusion criteria

We used the PICOS approach (population, intervention, comparison, outcome, study design) to analyze titles and abstracts.[21] We included studies that met all the following criteria: (1) population: the study included athletes (elite or recreational) who experienced a musculoskeletal injury without limits for age, sex, or level; (2) intervention: the study included an intervention group receiving either a topical or oral OTC medication; (3) placebo: the study included a group receiving a placebo medication; (4) outcomes: the study measured pain and functional improvements; (5) study design: the study was a randomized controlled trial. In order to meet the inclusion criterion of athlete, there needed to be specific words regarding the level of athlete, information about competition, or place of recruitment (at a game or practice).

Exclusion criteria were: (1) the study included a non-active population; (2) the study was done on animals; (3) the study used natural or alternative analgesics; (4) the study used analgesic medications for delayed onset muscle soreness (DOMS); (5) the study was done on induced injury or soreness; (6) the study was not available in English.

2.3 | Data extraction

Two reviewers extracted the following data from included articles: authors, year, sample size, setting, intervention characteristics, type of medication, placebo, dosage, pain measurement, point estimates, standard deviations (SD), and confidence intervals (CI). If authors only reported outcomes using figures, we used plot digitizer (http://plotdigitizer.sourceforge.net/) to extract data. This method was used for Åström & Westlin, 1992, Galer et al., 2000, Giani et al., 1989, May et al., 2007, Predel et al., 2004, Predel et al., 2016, and Wetzel et al., 2002. When authors reported data in multiple time points, we used the values for the "best day" characterized by the biggest difference in the outcomes between groups. We focused on the outcomes reported at rest; however, if authors only reported outcomes measured during activity, then those outcomes were used.

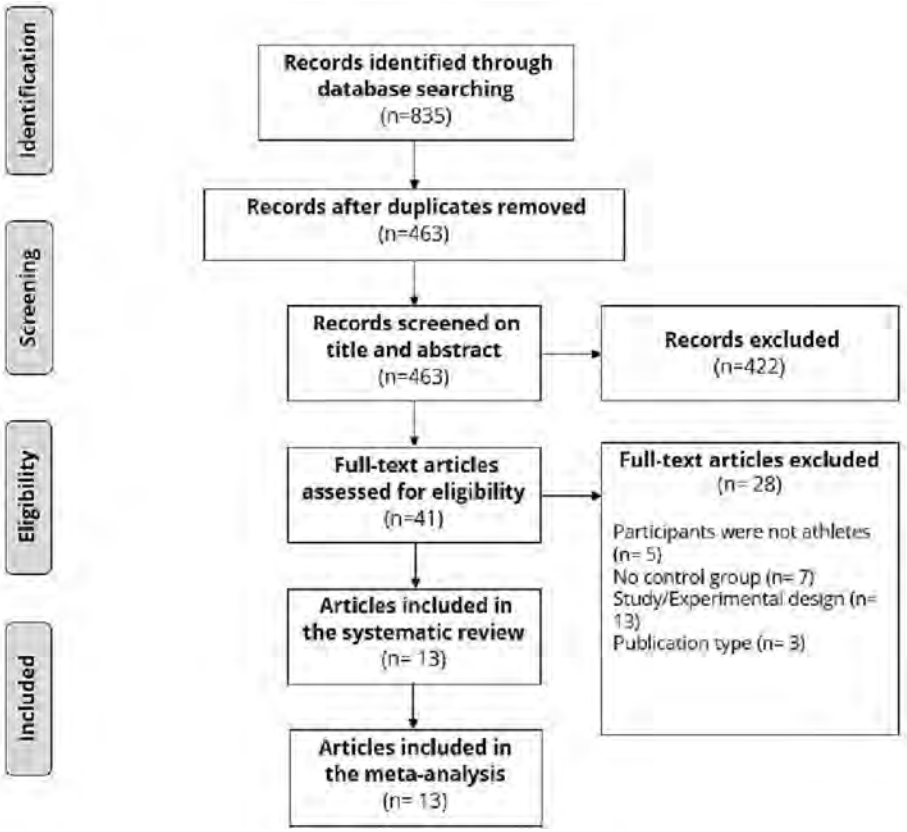

FIGURE 1 PRISMA flow diagram indicating process for identification, screening, eligibility, and inclusion of articles for the meta-analysis.

When authors reported standard errors (SE) instead of SD, we calculated the SD using the following formula: SD=SE*N. Similarly, when authors reported CI instead of SD or SE, we calculated the SD using the following formula: SD=N*(upper limit-lower limit)/3.92. We computed the intraclass correlation coefficient (ICC) to evaluate the agreement between reviewers in the data extraction process. We used Mendeley to manage the references, Rayyan QCRI to conduct the data screening process, and a spreadsheet to extract the data.

2.4 | Outcomes

We studied the effects of topical or oral analgesic medications when compared to a placebo in athletes. The independent variable was the type of medication, and the dependent variable was pain improvement measured using different scales including the visual analogue scale (VAS) for pain, the Numerical Rating Scale (NRS), and 4 or 5-point (Likert) function scales. The effect size (Hedges' g) was calculated for each study comparing the pain reduction with the oral or topical medication and the placebo. This was done for each individual study.

2.5 | Risk of bias assessment of individual studies

We assessed study quality using the Downs and Black checklist (DBC) (Appendix 3).[29] The DBC measures quality of reporting, external validity, internal validity (bias and confounding), and power. The maximal quality index (QI) is 28. The DBC is a 27-item checklist, in which each item can have a score of 1 or 0, except for question 5, which may score 2. We scored question 27 (power) as 0 or 1 the authors reported a power calculation. QI scores of >20 were considered good, 11–20 moderate, and <11 poor. We did not exclude any article based on the DBC scores. We evaluated the level of agreement between reviewers in the quality assessment using the ICC.

2.6 | Data synthesis – meta analysis

We used R 4.1.3 (https://www.r-project.org/) and the package meta 5.2–0 (https://cran.r-project.org/web/packages/meta/index.html) to conduct the meta-analyses.[30] We computed bias-corrected standardized mean differences (Hedges' g) of the change scores with 95% CI. We assumed that included studies were methodologically different, so we used an inverse-variance with random-effects model and the DerSimonian and Laird estimator to pool effect sizes and estimate between-study-variance (τ^2).[31] We created forest plots with 95% CI to graphically summarize the meta-analyses. We estimated statistical heterogeneity using Cochrane Q and the I^2 statistic; we interpreted I^2 as follows: 25%, 50%, and 75% reflecting low, moderate, and high heterogeneity, respectively.[32] We used funnel plots and Egger's regression tests to assess the risk of publication bias. We set an alpha level of 0.05 for all statistical tests.

3 | RESULTS

3.1 | Search results

We found 835 articles after using our search strategy (Appendix 2). After screening potential articles and removing duplicates, we used 13 articles (Figure 1) on this study. The agreement between reviewers in the data extraction process was ICC = 0.805 95%CI[0.643, 0.910].

3.2 | Risk of bias of individual studies

We reported DBC results for each study in Table 1: Characteristics of the Interventions and Participants. And 1230 DBC scores ranged from 13 to 25. Seven articles obtained QI scores above 20 in the DBC, and six articles obtained QI scores between 11 and 20 in the DBC. No study scored below 11 in the DBC. The agreement between reviewers when using the DBC was ICC = 0.840 95%CI[0.645, 0.933].

3.3 | Characteristics of the interventions and participants

There were 13 studies included in this article with 16 interventions. The studies done by Giani et al., 1989, Reynolds et al., 1995, and Wetzel et al., 2002, all had two interventions. We reported information for each article in Table 1. The articles involved 1304 participants from which 1273 received an intervention (410 females). A weighted average was used to calculate the average age or participants, which was 31.07 years, with the youngest participants being 17.5 years-old and the oldest being 58 years-old. Thirteen articles reported data from both males and females, but May et al. only analyzed data from males.

All articles reported an intervention compared to a placebo group.[22–28,33–38] Eight interventions used a topical medication, and five interventions used an oral medication. There was a wide range of intervention duration,

TABLE 1 Characteristics of the Interventions and Participants.

Study (year)	Participants (*n*)	Age (mean)	Information for athletic population	Intervention type	Intervention	Length of study	Pain scale	Downs and Black Score
Åstrom et al. (1992)	67; INT: 34 piroxicam (11 female); CON: 33 placebo (8 female)	Mean 35; INT: 18–58 piroxicam; CON: 20–57 placebo	Engaged in various sports, athletic performance, sports injuries, competitive level	Oral	INT: Piroxicam 40 mg 2 days and 20 mg thereafter; CON: Placebo	28 days (2 weeks mandatory, 2 weeks optional)	VAS 100 mm	12
Dupont et al., (1987)	61; INT: 30 ibuprofen (14 female); CON: 31 placebo (8 female)	INT: 23.9 ± 6.4 Ibuprofen; CON: 23.7 ± 5.7 placebo	Physically active individuals, Sports Medicine clinic	Oral	INT: 600 mg ibuprofen, 4 times per day; CON: Placebo (lactosa)	28 days	Scale 0–3	21
Galer et al., (2000)	213; INT: 106 diclofenac (28 female); CON: 107 placebo (37 female)	INT: 31.15 diclofenac; CON: 29.9 placebo	Sports related sprain, strain, contusion	Topical	INT: 1.3% diclofenac; CON: Placebo	14 days	VAS 100 mm	19
Giani et al., (1989)	45 (6 female)	Mean 20.87	Athletes, acute sports injuries	Oral	INT1: Diclofenac; INT2: Suprofen; CON: Placebo	7 days	VAS 0-100 mm	18
Malmgaard-Clausen et al., (2021)	68; INT: 33 naproxen (11 female); CON: 35 placebo (9 female)	INT: 41 ± 2.1 Naproxen; CON: 40.7 ± 1.7 Placebo	Active sports participants, return to sport	Oral	INT: Naproxen, 500 mg 2 times per day; CON: Placebo	1 year	NRS 0–10	17
May et al., (2007)	36; INT: 20 diclofenac; CON: 16 placebo (only men analyzed)	INT: 36 ± 12 Diclofenac; CON: 39 ± 10 Placebo	Long distance kayakers	Topical	INT: 2.5 g 1% diclofenac gel; CON: Placebo gel (sorbolene and 10% propyl alcohol)	5 days	Scale 1–5	21
Predel et al., (2017)	132; INT: 64 ibuprofen (31 female); CON: 68 placebo (39 female)	INT 33.2 ± 12.1 ibuprofen; CON: 30.8 ± 11.2 placebo	Acute injury in sport, immediate recruitment at sporting event (<3 h)	Topical	INT: Ibuprofen 200 mg plaster; CON: Placebo	6 days	VAS 0–100	25
Predel et al., (2004)	120; INT: 60 diclofenac (22 female); CON: 60 placebo (25 female)	INT: 31.6 diclofenac; CON: 31.7 placebo	Soccer, handball, and basketball competitions/ training camps	Topical	INT: 140 mg diclofenac sodium; CON: Placebo	7 days	VAS 0–100	25
Predel et al., (2016)	168; INT: 84 diclofenac (33 female); CON: 84 placebo (33 female)	INT: 33.39 ± 11.12 diclofenac; CON: 33.31 ± 11.45 placebo	Patients recruited on sports grounds	Topical	INT: 140 mg diclofenac sodium patch; CON: Placebo	7 days	VAS 0–100	24
Predel et al., (2018)	130; 66 ibuprofen (22 female); 64 placebo (20 female)	INT: 34.09 ibuprofen: CON: 30.08 placebo	Acute injury in sport, immediate recruitment	Topical	INT: 200 mg ibuprofen plaster; CON: Placebo	5 days	VAS 0–100	24

Study (year)	Participants (*n*)	Age (mean)	Information for athletic population	Intervention type	Intervention	Length of study	Pain scale	Downs and Black Score
Reynolds et al., (1995)	44; INT1: 13 meclofenamate (0 female); INT2: 16 diclofenac (1 female); CON: 14 placebo (0 female)	INT1: 33.8 ± 10.6 meclofenamate; INT2: 31.8 ± 9.9 Diclofenac; CON: 30.7 ± 7.9 Placebo	Acute sports related injury, sporting activity	Oral	INT1: 50 mg meclofenamate; INT2: 25 mg diclofenac; CON: Placebo	7 days	VAS 0–10	16
Steunebrink et al., (2013)	33; INT: 16 GTN (5 female); CON: 17 placebo (3 female)	INT: 31.9 ± 9.6 GTN; CON: 33.8 ± 10.5 Placebo	Recreational or competitive athletes, playing various sports	Topical	INT: Topical glyceryl trinitrate 5 mg; CON: Placebo	12 weeks	VAS 0–10 (reverse order)	19
Wetzel et al., (2002)	156; INT1: 54 escin 1% (17 female); INT2: 51 escin 2% (17 female); CON: 51 placebo (10 female)	INT1: 29.2 escin 1%; INT2: 31.3 escin 2%; CON: 30.7 placebo	Soccer, karate, handball competitions	Topical	INT1: Escin 1%, 5% diethylammonium salicylate, 5000 IU heparin; INT2: Escin 2%, 5% diethylammonium salicylate, 5000 IU heparin; CON: Placebo	24 h	VAS 0–10	24

from 24 h to 1 year. The post intervention pain level used to calculate the effect size was the day of the peak difference from the beginning of treatment. For most, this occurred within 2 weeks from the onset of pain.

3.4 | Meta-analysis

We observed a significant pooled effect size reflecting a reduction in pain outcomes for the topical treatment ($g = -0.64$; 95% CI [−0.89, −0.39]; $p < 0.001$). The meta-analysis for the topical treatment (Figure 2) presented high heterogeneity ($I^2 = 71\%$) indicating high variability between the effect sizes of the 8 included studies (with 9 interventions).

We did not observe a significant reduction in pain outcomes for the oral treatment ($g = -0.26$; 95% CI [−0.60, 0.17]; $p = 0.272$). The meta-analysis for the oral treatment (Figure 3) presented moderate heterogeneity ($I^2 = 55\%$) indicating moderate variability between the effect sizes of the 5 included studies (7 interventions).

When conducting a meta-analysis for the topical and oral treatments (Figure 4), we observed a significant pooled effect size ($g = -0.49$; 95% CI [−0.71, −0.27]; $p < 0.001$) with a moderate heterogeneity ($I^2 = 69\%$).

Funnel plots did not suggest risk of publication bias and the Egger's regression tests did not indicate funnel plot asymmetry for the topical treatment (Figure 4, $p = 0.699$) and for the oral treatment (Figure 5, $p = 0.461$).

We transformed the mean and standard deviations of the pain outcomes to a 100 mm VAS to favor comparability between outcomes (Figures 6 and 7).

4 | DISCUSSION

The objective of this study was to determine if topical and oral medications were effective at reducing pain compared to a placebo in injured athletes. As noted in the forest plots, the results of this meta-analysis suggest that topical analgesics are more effective compared to a placebo in reducing pain in an athletic population suffering from musculoskeletal injuries. It is important to note that the sustained injuries in this review were not associated with DOMS or induced pain but actual musculoskeletal injuries. When athletes suffer an injury, it is essential to know what medication would be effective in reducing pain. In addition, oral analgesic medications were not effective in reducing pain in injured athletes compared to a placebo. The forest plots also illustrate that both the topical and oral effect sizes are slightly more skewed to the left than the placebo medications, but only the topical is skewed enough to be statistically significant.

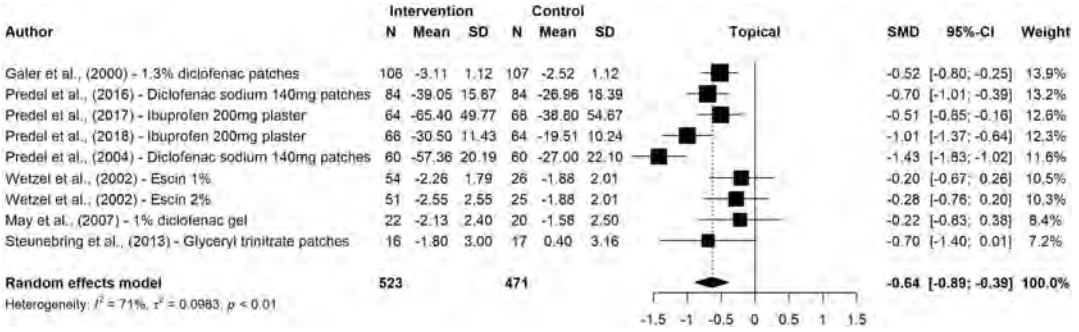

FIGURE 2 Forest plot indicating the efficacy of topical analgesic medication for injured athletes compared to a placebo. There was a significant improvement in pain in the athletes receiving the topical medication compared to the placebo ($p < 0.001$). Eight studies with nine interventions were analyzed.

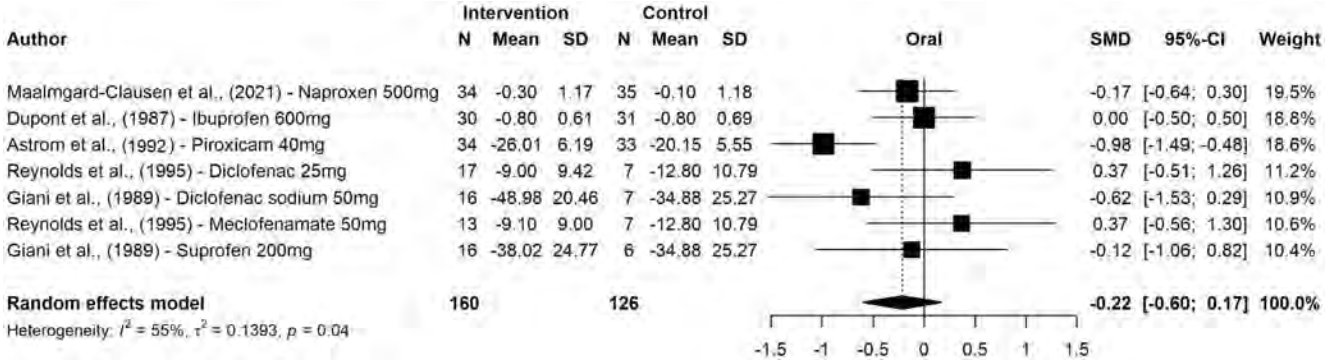

FIGURE 3 Forest plot indicating the efficacy of oral analgesic medication for injured athletes compared to a placebo. There was not a significant improvement in pain in the athletes receiving the oral medication compared to the placebo ($p = 0.272$). Five studies with seven interventions were analyzed.

4.1 | Why was the oral not effective compared to the placebo?

In this review, the group that received the oral placebo experienced a similar amount of pain reduction compared to the medication group. As mentioned earlier, many previous studies have shown effectiveness of oral medications over placebo. Thus, the analysis of the oral studies supports the idea that athletes have a higher placebo experience than nonathletes. However, the topical medications were overall more effective than the placebo, which contradicts this hypothesis. Though it has been previously demonstrated that athletes did not have a greater placebo effect than non-athletes in a study involving pain induction,[10] we expected the results of our study to be different as the subjects are injured athletes. The pain you experience from an injury will be different than pain induction because it will impact the return to play of the athlete. Furthermore, the mechanisms of injury are not the same when comparing sport-related injury to induced injury or DOMS.[39] It is thus not recommended to generalize the results from studies on the effect of medications on DOMS or induced injury to sport-related injuries.[39] As such, this current review only analyzes athletic injuries.

An individual can experience placebo analgesia because of verbal cues alluding to pain relief.[40] This can be due in part to the individual remembering previous experiences of pain relief.[40] Those who frequently use medication may be more conditioned to experience an analgesic effect similar to that of an active drug when a placebo is used.[40] As previously stated, athletes are subject to frequent injuries,[2] and analgesic medications that are available over-the-counter are frequently used by athletes.[7] The most common form of analgesic medication that athletes take are oral NSAIDs.[41] An athlete may thus be more used to taking oral analgesic drugs than topical for their injuries to help with their pain management and as such are conditioned to respond the same way to an oral placebo medication.

Since the 1960s, studies have suggested that the placebo effect is a result of the release of endogenous neuromodulators, such as opioids, cholescystokinin, cannabinoids, dopamine, as well as the activation of the vasopressin and oxytocin systems.[40,42] Placebo drugs have been shown to activate the rostral anterior cingulate cortex (rACC) and the orbitofrontal cortex (OrbC) on positron emission

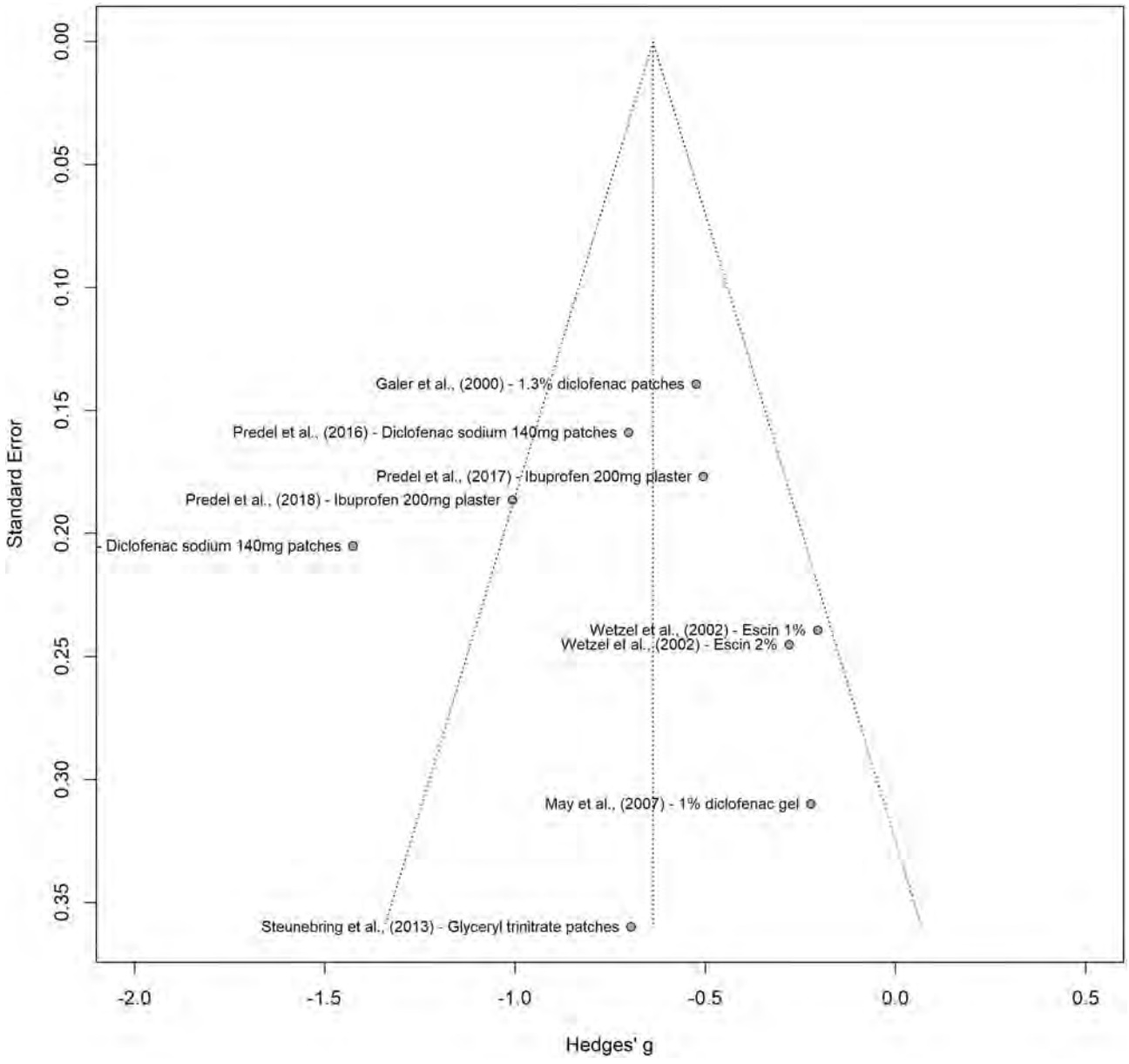

FIGURE 4 Funnel plot based on standardized effect sizes of the topical treatments.

tomography (PET).[43] Studies have shown that there is a descending pain-modulating pathway involving the rACC, the periaqueductal gray (PAG), and the rostral ventromedial medulla (RVM).[43] Functional magnetic resonance imaging of the brain during placebo analgesia showed decreased activity in areas involved in pain transmission such as the thalamus, the anterior insula (aINS), and the caudal rACC.[44]

4.2 | Previous studies comparing medication to placebo

To date, there have been various systematic reviews and meta-analyses analyzing the effectiveness of topical or oral analgesic medications on pain in adults compared to a placebo, but none exclusively done on athletes, and not all include a comparison of both topical and oral medications. There are varying results among these non-athlete studies. A systematic review and meta-analysis analyzing the effectiveness of oral and topical analgesic medications for ankle sprains stated that overall, both oral and topical medications were effective at reducing short term pain in adults.[45] A systematic review and meta-analysis studying the effectiveness of topical NSAIDs in acutely injured adults noted a significant overall effect size for diclofenac, ibuprofen, ketoprofen, piroxicam, and indomethacin compared to placebo.[46] Another review reported that among six randomized-controlled trials, topical and oral NSAIDS were statistically significant

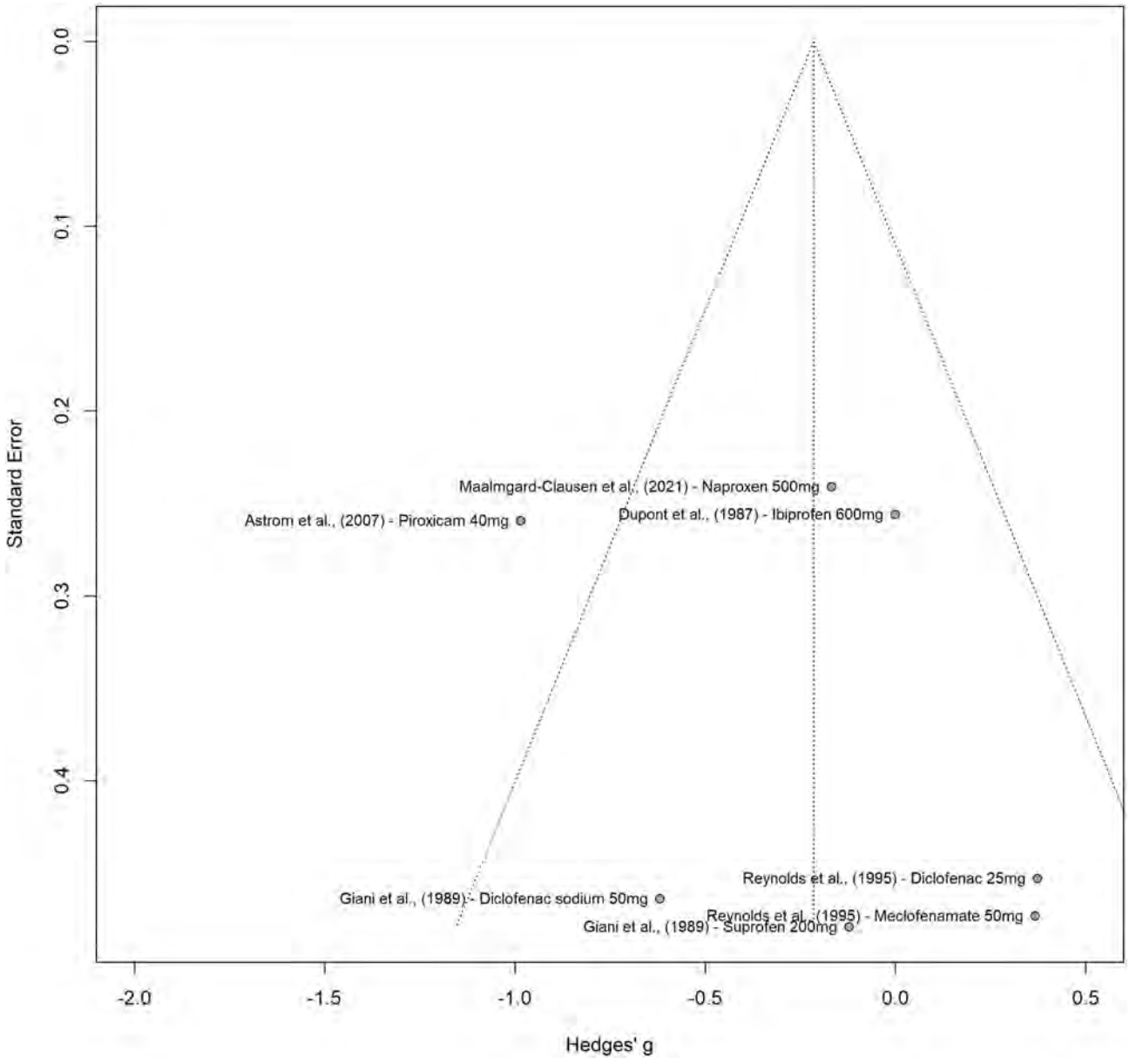

FIGURE 5 Funnel plot based on standardized effect sizes of the oral treatments.

over placebo medications at treating chronic lower back pain in adults.[47] They do however state that the quality of this evidence is low.[47] A review on lateral epicondylitis in adults showed low-quality evidence that there may be some benefit of topical and oral NSAIDs over placebo medication.[48] These reviews all include subjects suffering from acute or chronic pain, not experimentally induced pain or DOMS.

There have also been various studies on the effectiveness of topical and oral medications other than the reviews listed above. These studies compare topical to oral medications in various injured populations. A study on topical and oral ibuprofen in older adults with chronic knee pain showed that both formulations were equally effective at pain reduction.[49] A study measuring the effectiveness between topical and oral ibuprofen in acute soft-tissue injuries also concluded equal success.[50] Two systematic reviews showed no difference in effectiveness between oral and topical NSAIDs for acute and chronic pain.[46]

As our review exclusively looks at the effectiveness of analgesic medications in an athletic population, the results were hypothesized to be different than the regular population. The following are the reasons why this may be.

Humans often use analgesic medications to reduce pain but are also able to inhibit pain through their own endogenous pain-inhibition system.[51] There are numerous ways in which this occurs, including use of placebo medications or the activation of this system through conditioned pain modulation (CPM). Chronic pain may develop as a result

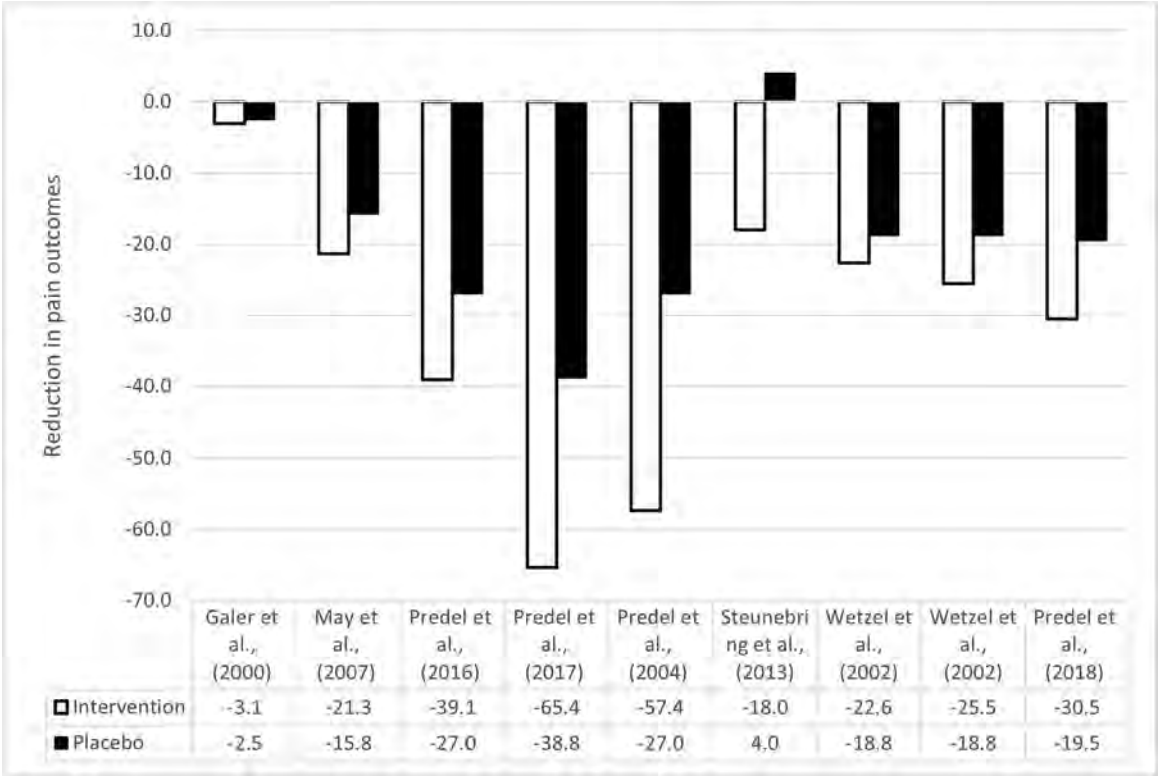

FIGURE 6 Reduction in pain outcomes for topical treatment versus placebo based on change scores in a 100 mm VAS for the topical treatment. The pain ratings have been adjusted to the VAS.

of reduced endogenous pain inhibition.[52] One systematic review demonstrated that chronic pain patients had a reduced CPM.[53] This was demonstrated in the non-athletic population. Conversely, it has been shown that endurance athletes have a higher CPM effect than non-athletes.[54–56] There is a high prevalence of sports injuries among athletes.[2] These injuries can be acute or chronic, and can be accompanied by pain.[2] These athletes will oftentimes play through their pain.[57] Athletes have been shown to have a higher pain tolerance than non-athletes.[10,11] These factors may contribute to the higher CPM seen in athletes. This further suggests that athletes have a stronger endogenous pain-inhibition system than non-athletes. It has been suggested that CPM and the placebo effect occur via the same mechanism.[58,59] As such, it is plausible to believe that athletes would also have a higher placebo effect than non-athletes.

4.3 | Mechanisms of action of the medications

The medications used in the studies included in this review were NSAIDs (ibuprofen, piroxicam, naproxen, and diclofenac) as well as diethylammonium salicylate with Escin, and triglyceryl nitrate, which all reduce pain in different ways. NSAIDs reduce pain by inhibiting the cyclooxygenase (COX) enzyme activity.[60,61] COX enzymes are responsible for the production of prostaglandins following tissue injury.[61] COX is responsible for the conversion of arachidonic acid into thromboxanes, prostaglandins, and prostacyclins.[62] Thromboxanes are required for platelet aggregation, while prostaglandins are vasodilators, increase the hypothalamus temperature, and have a role in pain relief.[60] By blocking these actions, NSAIDs decrease pain.[60]

The isoenzymes COX-1 and COX-2 are the ones that are typically targeted by NSAIDS.[60] COX-1 enzymes are essential in the body, while COX-2 enzymes are present during anti-inflammatory response.[63] Some NSAIDs are selective and target only COX-2,[63] but all of the NSAID medications in this present study are non-selective and target both COX-1 and COX-2 enzymes. The mechanism of action for NSAIDs are the same for both oral and topical medications.

Diethylammonium salicylate is a type of rubefacient which is thought to decrease pain by causing counter-irritation to the skin.[64] This counter-irritation causes a vasodilation, resulting in a warming sensation.[65] This drug is related to NSAIDs but works by a different mechanism when applied topically.[65] The cutaneous irritation produces sensory nerve irritation, which is believed to decrease pain in the musculoskeletal structures innervated by the same nerves.[65] Escin has been shown to decrease

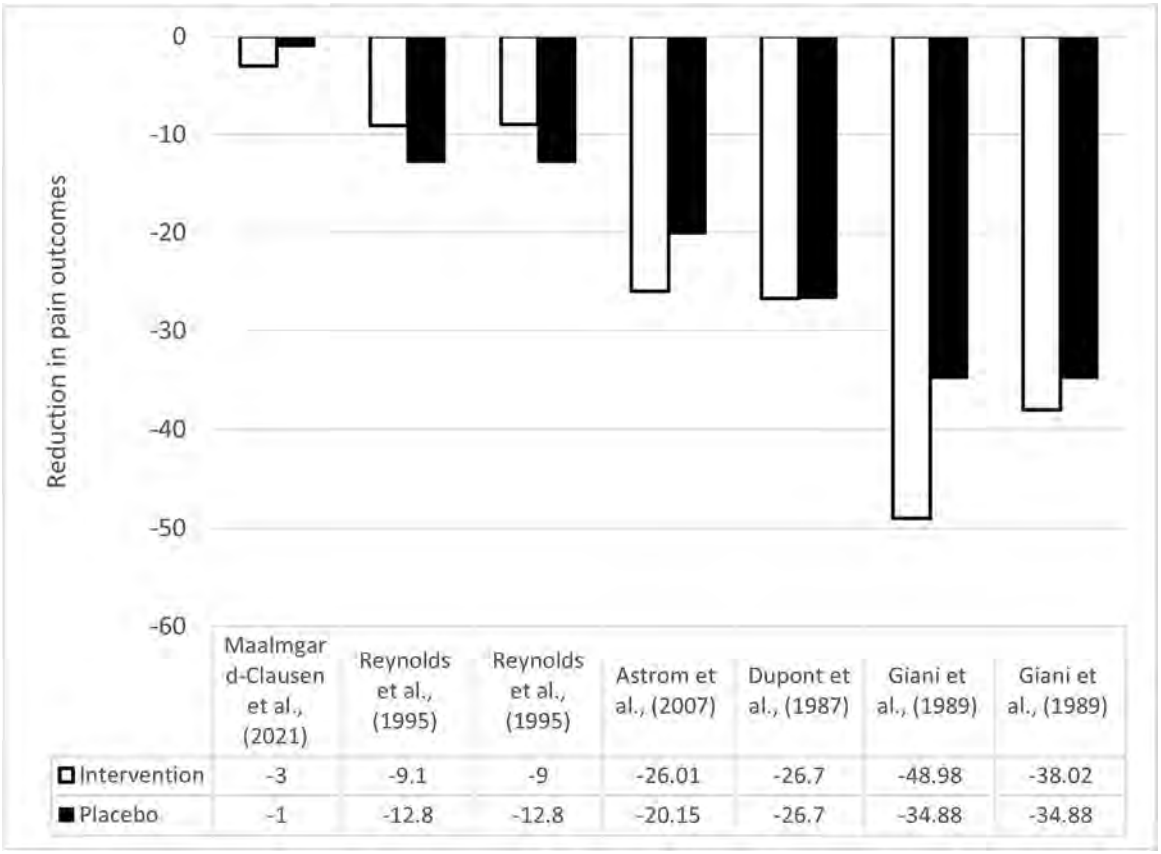

FIGURE 7 Reduction in pain outcomes for oral treatment versus placebo based on change scores in a 100 mm VAS. The pain ratings have been adjusted to the VAS.

inflammation, but the mechanism in humans is still unclear.[66]

Glyceryl trinitrate (GTN) liberates nitric oxide (NO) in the tissue.[67] NO is thought to influence tendon healing by being involved in processes such as blood flow, host defense, and collagen synthesis.[68]

4.4 | Why would topical medications be more effective than oral?

While oral NSAIDs act systemically to inhibit COX activity, topical analgesics act locally to reduce pain. An acute musculoskeletal injury is accompanied by a local inflammatory reaction.[27] Oral NSAIDs only target the affected area after large quantities of the drug enter systemic circulation, whereas topical NSAIDs can deliver direct relief.[27] Topical medications also interact with nociceptors in the outer layers of the skin at the site of the injury (Choi et al., 2020). They penetrate the stratum corneum in the epidermis to reach unmyelinated A δ and C-fibers, which transmit the sensation of pain.[69] This direct interaction with the pain site may offer an explanation as to why the topical medication was more effective than the oral medications in this study.

There are some side effects of oral NSAIDs. By acting on prostaglandins, NSAIDs can adversely affect the gastric mucosal barrier, renal blood flow, endothelial tone, circulatory system, kidneys, and liver.[70,71] The rationale behind topical NSAIDs is that they can act locally to inhibit COX activity with minimal systematic effect.[70] Topical NSAID application does reach high enough levels to inhibit COX-2 activity, all while being found at low levels of plasma concentration.[70,71] Because of this, there should be less adverse effects with the use of topical NSAIDs.

The other types of medication in this review, diethylammonium salicylate and glyceryl trinitrate, are used exclusively topically for pain management.

4.5 | Variability in studies in this review

The forest plot shows that there is a high heterogeneity among the topical and oral studies. The variance in these studies could thus be due to something other than chance. The topical studies had generally higher sample sizes than the oral studies, and there were more topical studies included in the analysis which met the search criteria.

None of the oral medication studies except Åström & Westlin, 1992, were statistically significant. The confidence

intervals shown on the forest plot were high for each oral study, indicating less precision.

There are several reasons for the variability among the studies. The studies measured pain levels on different days. Some studies were conducted over the course of several months, and others just over a few days. This could contribute to the variability in the results, as the natural course of pain is such that pain may improve on its own the more time has elapsed since the injury date. Some studies allowed the athletes to receive concurrent therapy such as the use of ice, physical therapy, or rescue medication (typically acetaminophen). As such, the decrease in pain can be affected by other factors than solely the medication used. The use of concurrent therapies is possibly due to ethical concerns regarding withholding treatment from participants. Other factors that could affect the variability in the results are that there are different injuries being studied, as well as different pain levels at the beginning of the study among groups.

Additional factors that may affect the variability of the studies are the type of medication used and the location of application for topical analgesics. The studies within this review used different types of medications, thus there could be differences in the efficacies. Furthermore, it has been suggested that the bioavailability of the topical drug used differs depending on the location of the application.[72] In this study, ketoprofen applied to the back and arm produced statistically significantly higher plasma levels than in the knee of male subjects.[72] Some studies in this review observed the effect of a certain drug on a common type of injury, but many other included various musculoskeletal conditions. Thus, it is possible that the topical drug applications may have been more effective with some injuries and others less so.

4.6 | Future directions

To show that a medication is superior to a placebo, it is best practice to include an experimental drug group, a placebo group, and a natural history (NH) group, taking no medication at all.[73] The purpose of the NH group is to show that the reduction in pain is not due to other factors such as the natural course of the injury or spontaneous healing.[73] None of the studies in this review included an NH group, presumably for the ethical reason of not withholding a treatment that could potentially help the individual's pain. As such, there are two speculations that we can make. The first is that if athletes do not in fact experience the placebo effect as highly as non-athletes do even in sport-related injuries, then the insignificant results between the experimental and placebo groups for oral medications could be because neither are truly effective, and that the injury took its natural healing course. If the results of the Geisler study on pain provocation cannot be extrapolated to sustained injuries in athletes, then the results of this study would show that the experimental analgesic oral drugs do not reduce pain statistically significantly more than placebo medications.

4.7 | Limitations

As stated previously, there were more topical than oral studies used in this meta-analysis. Many oral medication studies in athletes were excluded for reasons such as not including a placebo group, or not including enough data to be able to carry out the meta-analysis. Most subjects in all the studies used are male, thus we were unable compare differences in male and female response to analgesic medication. There was also a wide age range among the study participants. Age and sex may influence pain, so it would have been favorable to have less variation in these variables. There was a range in the level of athlete that was included in the study (from recreational to elite), as well as many different types of injuries in the study participants. The dose of medication or length of treatment also varied among the studies used in the meta-analysis.

5 | CONCLUSION

Topical analgesic medications are more effective than oral medications at reducing pain in athletes. There are less reported adverse effects with the use of topical medications. If given the choice, athletes should elect to take topical medications instead of oral medications to help reduce pain after injury.

6 | PERSPECTIVE

Athletes will often take medications for their injuries and may do so without guidance due to OTC medications being readily available without prescription.[3,7,8] As such, they should be aware of which medication will be the most effective for them with the least amount of adverse effects. Sports medicine staff, including athletic therapists/trainers, should also be aware of the ideal medication to recommend for the injured athlete under their care. Traditionally, athletic therapists or trainers are not involved when it comes to the recommendation of medication for their athletes, as it lies outside of their scope of practice. However, this does not prohibit or discourage athletes from continuing the practice of self-medication, as previously stated. If an athlete does not have a team

doctor, then their team therapist would likely be the next person that they would be communicating with for injury management. If athletic therapists are made aware of the results of this study, then they can help to better guide their athletes with medication usage.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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APPENDIX 1

Search strategy.

Database	Search strategy
Web of Science	TOPIC: (comparison OR efficacy) AND TOPIC: (medication OR drug OR analgesic) AND TOPIC: (ketorolac OR Toradol OR anti-inflammatory OR NSAID OR ibuprofen OR acetaminophen OR paracetamol OR aspirin OR acetylsalicylic acid OR corticosteroid OR diclofenac OR piroxicam OR indomethacin OR naproxen OR ketoprofen) AND TOPIC: (placebo) AND TOPIC: (athlete OR sport OR game OR athletic injuries OR sports medicine OR athlet* OR injur*) AND TOPIC: (oral OR topical)
Ovid/Medline	(comparison OR efficacy) AND (medication OR drug OR analgesic) AND (ketorolac OR Toradol OR anti-inflammatory OR NSAID OR ibuprofen OR acetaminophen OR paracetamol OR aspirin OR acetylsalicylic acid OR corticosteroid OR diclofenac OR piroxicam OR indomethacin OR naproxen OR ketoprofen) AND (placebo) AND (non-steroidal) AND (athlete OR sport OR game OR athletic injuries OR sports medicine OR athlet* OR injur*) AND (oral OR topical)
SPORTDiscus	(comparison OR efficacy) AND (medication OR drug OR analgesic) AND (ketorolac OR Toradol OR anti-inflammatory OR NSAID OR ibuprofen OR acetaminophen OR paracetamol OR aspirin OR acetylsalicylic acid OR corticosteroid OR diclofenac OR piroxicam OR indomethacin OR naproxen OR ketoprofen) AND (placebo) AND (non-steroidal) AND (athlete OR sport OR game OR athletic injuries OR sports medicine OR athlet* OR injur*) AND (oral OR topical)
PubMed	(comparison[Title/Abstract] OR efficacy[Title/Abstract]) AND (medication[MeSH Major Topic] OR drug[Title/Abstract] OR analgesic[Title/Abstract]) AND (ketorolac[Title/Abstract] OR Toradol[Title/Abstract] OR anti-inflammatory[Title/Abstract] OR NSAID[Title/Abstract] OR ibuprofen[Title/Abstract] OR acetaminophen[Title/Abstract] OR paracetamol[Title/Abstract] OR aspirin[Title/Abstract] OR acetylsalicylic acid[Title/Abstract] OR corticosteroid[Title/Abstract] OR diclofenac[Title/Abstract] OR piroxicam[Title/Abstract] OR indomethacin[Title/Abstract] OR naproxen[Title/Abstract] OR ketoprofen[Title/Abstract]) AND (placebo[MeSH Major Topic) AND (non-steroidal[Title/Abstract]) AND (athlete[MeSH Major Topic] OR sport[MeSH Major Topic] OR game[Title/Abstract] OR athletic injuries[MeSH Major Topic] OR sports medicine[MeSH Major Topic] OR athlet* OR injur*) AND (oral[Title/Abstract] OR topical[Title/Abstract])

APPENDIX 2

Records by database.

Database	Records identified using the search strategy
PubMed	237
Scopus	185
Web of Science	235
SPORTDiscus	178
Total	835

APPENDIX 3

Downs and Black Checklist.

Article	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q23	Q24	Q25	Q26	Q27	Total
Galer et al. (2000)	1	1	1	1	0	1	1	1	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	1	1	19
Predel et al. (2004)	1	1	1	1	2	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	25
Astrom & Westlin (1992)	1	1	1	1	0	1	1	0	0	0	0	0	0	1	1	1	0	1	0	1	0	0	1	0	0	0	0	12
Dupont et al. (1987)	1	1	1	1	2	1	1	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	1	0	21
Malmgaard-Clausen et al. (2021)	1	1	1	1	0	1	1	0	0	0	0	0	0	1	1	1	1	1	0	1	1	1	1	1	0	1	0	17
Reynolds et al. (1995)	1	1	1	1	0	1	1	1	0	1	0	0	0	1	1	0	0	1	0	0	1	1	1	0	0	1	1	16
Giani et al. (1989)	1	1	1	1	0	1	1	0	0	1	0	0	0	1	1	0	0	1	0	1	1	1	1	1	1	1	1	18
May et al. (2007)	1	1	1	1	2	1	1	0	1	1	1	1	0	1	1	1	0	0	1	0	1	1	1	1	0	1	0	21
Predel et al. (2017)	1	1	1	1	2	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	25
Predel et al. (2016)	1	1	1	1	2	1	1	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	24
Predel et al. (2018)	1	1	1	1	2	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	24
Steunebrink et al. (2013)	1	1	1	1	2	1	1	1	0	0	0	0	0	1	1	1	1	1	0	1	1	1	1	1	0	0	0	19
Wetzel et al. (2002)	1	1	1	1	2	1	1	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	24