Analgesic Management of Pain in Elite Athletes: A Systematic Review

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Abstract

Objective: To identify the prevalence, frequency of use, and effects of analgesic pain management strategies used in elite athletes.

Design: Systematic literature review

Data Sources: Six databases: Ovid/Medline, SPORTDiscus, CINAHL, Embase, Cochrane Library, and Scopus.

Eligibility criteria for selecting studies: Empirical studies involving elite athletes and focused on the use or effects of medications used for pain or painful injury. Studies involving recreational sportspeople or those that undertake general exercise were excluded.

Main Results: Of 70 articles found, the majority examined the frequency with which elite athletes use pain medications, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, anesthetics, and opioids. A smaller set of studies assessed the effect of medications on outcomes such as pain, function, and adverse effects. Oral NSAIDs are reported to be the most common medication, being used in some international sporting events by over 50% of athletes. Studies examining the effects of pain medications on elite athletes typically involved small samples and lacked control groups against which treated athletes were compared.

Conclusions: Existing empirical research does not provide a sufficient body of evidence to guide athletes and healthcare professionals in making analgesic medication treatment decisions. Based on the relatively robust evidence regarding the widespread use of NSAIDs, clinicians and policymakers should

carefully assess their current recommendations for NSAID use and adhere to a more unified consensus-based strategy for multi-disciplinary pain management in elite athletes. In the future, we hope to see more rigorous, prospective studies of various pain management strategies in elite athletes, thus enabling a shift from consensus-based recommendations to evidence-based recommendations.

Introduction and Background

Sports injury is common, and subsequent pain is a normal physiological accompaniment of such injury. Pain is defined as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[1] Furthermore, pain can reflect the mechanism of injury and be influenced by biopsychosocial factors. The experience of pain is shaped by neurophysiological, cognitive, affective, social, and environmental influences. Given these complexities, and the absence of clear clinical guidelines, pain management strategies vary internationally and often do not reflect an understanding of the cause and type of pain experienced by athletes.

Elite athletes, such as professional athletes and athletes competing internationally, likely experience pain and pain treatment differently than people undertaking general exercise.[2-4] Elite athletes may use oral, injectable, and transdermal non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, injectable and trans-dermal anesthetics, as well as cannabinoids, anti-depressants, anxiolytics, muscle relaxants, and anti-convulsants.[5-8] Furthermore, because of their unique training and competition regimens, and their access to specialized medical support, elite athletes may be more likely to use multiple agents, receive analgesics from multiple sources, or use analgesics to prevent pain.[5, 9-11] However, efforts to prevent or manage pain solely with medications can increase risk of adverse effects while failing to resolve underlying pain conditions.[12-15] In addition, some substances used for pain are

listed on the World Anti-Doping Agency (WADA) List of Prohibited Substances and Methods, including some opioid analgesics and cannabinoids.[15]

Despite indications that medication use to relieve and prevent pain is widespread among elite athletes,[5, 9, 11, 16-18] there has never been a comprehensive undertaking to identify the usage frequency and effect of pain medications among elite athletes. A systematic literature review focused on elite athletes can provide a foundation for clearer, more consistent, and evidence-based recommendations regarding athletes' medication use, healthcare professionals' medication prescribing, and anti-doping policy. Therefore, the objective of this study was to conduct a systematic literature review to identify the usage frequency and effect of analgesic pain management strategies in elite athletes. This review also served as a foundation for some of the key questions examined at the International Olympic Committee's (IOC) 2016 Consensus Meeting on Pain Management in Elite Athletes.[19]

Methods

We followed the PRISMA guidelines[20] to conduct a systematic review of the peer-reviewed literature to examine what is currently known about medication for pain management in elite athletes. Our search joined three general search concepts: (1) *pain or analgesic treatment modalities* AND (2) *athlete/sport* AND (3) *elite*. With this, we aimed to retrieve literature related to the use and effect of medications for pain or painful injuries in an elite athlete population. Between February 2 and 14, 2017, we searched six literature databases, Ovid/Medline, SPORTDiscus, CINAHL, Embase, Cochrane Library, and Scopus (see Appendix for detailed search strategy). This search provided an update to a search we conducted in November 2015, which served as a reference to the IOC Consensus Meeting on Pain Management in

Elite Athletes. We searched each database using a controlled vocabulary and keywords that represented the three general search concepts mentioned above (see Appendix for full syntax). We restricted our searches to English language and human studies. We did not restrict to a specific date range. In addition to the primary searches, we examined supplemental sources for qualifying articles. These sources included the reference lists of systematic review articles returned by our searches.

After retrieving article results for each database and supplemental sources, we conducted an initial review of titles and abstracts to identify relevant articles. We used a PICO (Population, Intervention, Comparison, Outcome) approach as a starting point for our inclusion criteria, though our review is broader and not all included studies simply map to each PICO criterion.[21] In particular, our relevant Population was elite athletes; relevant Interventions were analgesics or other medications used for pain; relevant Comparisons were any; and relevant Outcomes were any outcomes related to prevention or treatment of pain or painful injuries. We included empirical studies involving elite (i.e., Olympic, Paralympic, professional, collegiate, or other elite) athletes where at least one of the article's foci was on the use, efficacy, or effectiveness of medications used for pain or painful injuries. Studies involving "other elite" athletes were those identified by the authors' using keywords such as "elite" or "competitive." Such studies often involved nationally-recognized athletes, such as those supported by national Olympic training programs or youth national teams. However, we also included a small number of studies where the authors simply identified study participants as competitive and article context suggested involvement of elite athletes. We excluded studies that were not empirical, commentaries, non-systematic literature reviews, and studies that included fewer than 10 elite athlete participants. We also excluded articles focused on pain medications that are no longer used in humans.

Following the initial title and abstract review, we examined the full text of remaining articles to determine final inclusion and to code each article for relevant features. Three reviewers first coded a 20% sub-sample of the total articles and discussed differences to increase subsequent consistency in coding. The remaining articles were each coded by a single reviewer. Then, the three coders met as a group to review final article inclusion and discuss any uncertainties that arose during individual coding. When coding the articles, we extracted the publication year, study design, risks of bias, sample size, population (including sport, athlete gender, and athlete country), interventions, type of pain/injury, location of pain/injury, duration of pain, study outcomes, and authors' interpretation of the intervention effect (desirable, undesirable, none, unknown, or not applicable). We synthesized results be generating summary statistics and qualitative interpretations of the coding results and in-depth article reading.

Results

Article inclusion

Our searches found 5,321 total articles, and 4,700 after duplicates were removed (Figure 1). We excluded 4,589 articles after reviewing titles and abstracts. We most commonly excluded articles because they were not empirical or because they focused on non-athlete or non-elite athlete populations. Next, we reviewed the full text of the remaining 111 articles and excluded 49 of those. We excluded articles in this final stage because further analysis determined they involved non-elite athletes, were non-systematic reviews, were not empirical, did not involve pain medications currently used in humans, or were clearly duplicative of articles or data already included. Finally, we included 8 other qualifying articles from other sources. Together, this process resulted in a final set of 70 articles for analysis.[5, 8-11, 16-18, 22-83]

Overview of studies

The 70 articles were published between 1975 and 2016. In 20 articles, the athletes studied originated from multiple countries. Fourteen articles involved athletes from only the United States of America (USA), the most from a single country. Also, multiple studies involved athletes from Argentina, Australia, England, Finland, Norway, Germany, and Italy, with other countries represented in a single article only. Thirty-two studies involved multiple sports. Sixteen of the single-sport studies involved football (soccer). Other sports found in multiple articles include American football, basketball, rugby, cycling, hockey, track and field, volleyball, handball, and judo. In terms of athlete level, 25 articles involved professional athletes or a mix of professional and other elite athletes. Nine articles involved collegiate or a mix of collegiate and other elite athletes. Eleven articles involved Olympic or a mix of Olympic and other elite athletes. One article focused solely on Paralympic athletes. The remaining articles focused on other elite athletes. Athlete gender was sometimes not specified and could not be clearly inferred from the information presented in 15 articles. However, 23 articles involved only male athletes, and 33 articles clearly involved a mix of male and female athletes.

Studies of medication use

The largest group of included articles (n=45) reported frequency of medication use by athletes across a range of sports. Often, these studies described analyses of doping control forms, therapeutic use exemptions, pharmacy services, or other reports collected during major sporting events, such as the Olympic Games,[10, 22, 27-29, 40, 77] Paralympic Games,[22, 76] Pan-American games,[30, 81] Asian Games,[57] and Fédération Internationale de Football Association (FIFA) tournaments.[11, 17, 18, 26, 58, 75, 80] Other studies surveyed collegiate athletes.[38, 46, 64, 74, 82] In addition, some studies provided estimates through analysis of drug chemistry results (in- or out-of-competition).[26-28, 32, 57, 65]

Oral or non-specific route NSAIDs

NSAIDs are the most frequently studied and reported to be the most frequently used pain medication. Table 1 provides an overview of 25 studies that report oral (or non-specific route) NSAID use rates. We were challenged to compare frequencies across all articles because studies reported estimates using different techniques and over different time periods, such as in the last 12 months, in season, in the last 7 days, or during a given competition. Also, articles varied with respect to the mix of sports reported on and in the source of the medication data, such as physician prescribed, athlete self-report, laboratory testing, or pharmacy records. On one hand, some articles presented relatively low prevalence of NSAID use, including 2.4% of urine samples containing traces of NSAIDs at the 1988 Olympic Winter Games,[28] 6.7% of Finnish Olympic athletes prescribed NSAIDs in the last 7 days,[22] 9.8% of Paralympic athletes who declared NSAID use on doping control forms during the Athens 2004 Games,[76] and 11.1% of Olympic athletes who declared NSAID use on the doping control forms during the Athens 2004 Games.[77] On the other hand, some articles described relatively high rates of use, including 100% use in non-traumatic injuries suffered during an international cycling race (n=16),[83] 93% use in the past year among Italian professional football players,[69] over 50% use during the course of an international football tournament,[11, 17, 18, 75, 80] and 50% use among collegiate American football players over the course of a season.[38] Studies consistently suggested that NSAID use rates are concerning for myriad reasons, including concurrent use of multiple NSAIDs, multiple routes of administration, higher than the manufacturer's recommended dosing, use for prophylaxis of pain, limited evidence-based clinical guidance, adverse effects, and limited evidence regarding effects on injury healing.[5, 10, 11, 17, 29, 38, 40, 58] However, some male former athletes may actually be less likely to use NSAIDs when compared with age-matched controls.[43] And, there is some indication that the frequency of NSAID use decreased during the 2014 FIFA Men's Football World Cup compared to previous years' tournaments.[80]

Injectable pain medications

Compared to oral NSAID use, fewer studies reported on injectable NSAID use. Among Paralympic athletes, 9.8% reported using NSAIDs on the doping control forms, with 11.6% of those administered via injection.[76] Also, 93% of National Football League (NFL) physicians in the USA reported administering injectable Ketorolac as often as once per week during the 2000 season, with 21% of teams reporting an adverse experience.[71] Similarly, across many sports, 79% of American sports medicine physicians reported administering injectable Ketorolac to collegiate athletes and 43% reported administering to professional athletes, with 12% reporting an adverse reaction.[8] Finally, an estimated 31% of football players received NSAID injections prior to matches during the 1996 African National Cup.[9]

Some studies reported injectable anesthetic and/or corticosteroid use. However, like with NSAIDs, the approach to measuring and reporting of this practice varied. For example, injectable anesthetics and injectable corticosteroid use were sometimes combined and reported in a single use estimate. In other studies, injectable and oral corticosteroids were combined and reported in a single use estimate. A study of Paralympic athletes reported injectable corticosteroid use in 0.1% of athletes and injectable anesthetic use in 1.9% of athletes.[76] An estimated 13.5% of hamstring injuries in NFL players are treated with injectable corticosteroids.[44] During the 2014 FIFA Men's Football World Cup, team physicians reported that 2.6% of athletes used injectable anesthetics and 3.1% used intraarticular or periarticular injectable corticosteroids.[80] Similarly, between 2.2% and 5.7% of male athletes used either injectable anesthetics or injectable corticosteroids at each of the FIFA Futsal World Cup tournaments between 2002 and 2012.[58]

Opioid analgesic medications

Most studies that asked athletes about, or tested samples for, opioids reported use rates below 1% of athletes.[26, 28, 32, 35, 57, 58, 65, 76, 79] A study of pharmacy records from team South Africa during the Athens 2004 Olympic Games found an average of only 1.54 tablets of opioid-containing analgesics (e.g., paracetamol/ibuprofen/codeine) were dispensed per athlete.[10] Similarly, few athletes report being offered or knowing someone who has used opioids.[23] However, one small study reported tramadol use in 3.3% of 30 elite cyclists over the previous three months.[45] Also, 5.6% of Nigerian professional athletes reported using codeine at some point in the past.[52]

Other medications used for pain

Reported rates of non-NSAID oral analgesic medications ranged from 0.4% of players at the 2007 under-20's World Cup[11] to 20% among elite Italian cyclists in the previous three months.[45] Often, such medication use was reported simply as "analgesic" rather than specifying what types of non-NSAID medications, such as paracetamol. An analysis of over 18,000 doping control forms between 2002 and 2005, found less than 1% of athletes had used anesthetics, such as lidocaine, in the past three days.[79] Similarly, 1.6% of urine samples analyzed during the 1988 Olympic Winter Games tested positive for lidocaine.[28]

Similar to NSAIDs, estimates of corticosteroid use varied, partially due to different approaches to measurement. Rates of any corticosteroid use (route of administration not specified further) in the last three days as assessed by doping control forms in the mid 2000's includes estimates between 1%[67] and 6.2% - 9.2%.[79] Corticosteroid use among elite cyclists was estimated at 15.8%.[34] Surveys of physicians about oral corticosteroids, either in or out of competition, found that 83.9% of team physicians

prescribe to NFL players,[78] and 32% of physicians prescribe to collegiate athletes.[46] Finally, three other studies of collegiate athletes surveyed use of all non-prescription over-the-counter medications combined, including NSAIDs, paracetamol, and others.[64, 74, 82] These studies found use of over-the-counter analgesic medications by 58% to 73% of athletes. These studies also reported athletes lacked awareness about adverse effects,[74] had significant external influence to use pain medications, and frequently misused pain medications,[74, 82] especially collegiate American football players.[64]

Studies assessing effects of medications

Randomized Controlled Trials

We reviewed eight randomized controlled trials (RCTs), all but one of which was published in 1990 or earlier and had sample sizes of 13-60 athletes (Table 2). Five of the eight RCTs compared the effect of two different oral NSAIDs on acute pain when treating various injuries.[33, 48-50, 61] Each study included pain as a primary outcome, measured by self-report numeric rating or visual analog scale. Secondary outcomes including swelling,[48] return to sport,[49] and physical function.[49] These studies all found differences in the efficacy of different NSAIDs. Flurbiprofen was more efficacious than aspirin in terms of pain reduction and return to play related to acute lower limb soft tissue injuries.[50] Furthermore, piroxicam was more efficacious than tenoxicam[33] and naproxen[48] in reducing pain from an acute sport-related ligament sprain. Piroxicam was also shown to be more efficacious than ibuprofen in reducing acute pain and increasing active and passive physical function in athletes with sprains, strains, and other soft tissue injuries that had caused functional disability.[61] In addition to the RCTs involving oral NSAIDs, one study of collegiate athletes found diflusinal, a salicylic acid derivate, was equally efficacious in reducing pain, tenderness, and swelling due to acute injury as paracetamol combined with codeine.[41]

The most recent RCT, from 2006, examined elite athletes with chronic patellar tendinopathy and found sclerosing injections of polidocanol to be more effective in improving pain scores and function assessments than lidocaine with epinephrine injections.[36] Finally, one RCT compared the effect of naloxone versus placebo in non-injured athletes.[66] The study found weak evidence to suggest that naloxone may reduce affective components of pain but not sensory, evaluative, supplemental, or overall pain intensity.[84]

Observational studies

Twelve of 14 observational studies evaluated the effects of non-NSAID injectable therapies, which included corticosteroid injections,[39, 42, 44, 68] injectable or local anaesthetics,[51, 53, 54, 62] and, in chronic situations, regenerative dextrose injections,[72, 73] and sclerosing injections[24, 37] (Table 3). These studies focused on groin pain,[39, 51, 62, 72, 73] hamstring injury,[44, 68] lumbar disc herniation,[42] patellar tendinopathy,[24, 37] or a mix of injuries and pain.[53, 54] Four studies reported on acute pain or injury.[39, 42, 53, 62] Four studies reported on either chronic pain or chronic and subacute pain combined.[24, 68, 72, 73] Four studies were non-specific about pain chronicity.[37, 44, 51, 54] The majority of the studies concluded there were positive effects of the primary therapy on reduction of pain or related outcomes. Studies finding negative or null results often suggested the need to evaluate the risks and benefits of the therapies on a case-by-case basis. However, in terms of study design, none of the studies of injectable medications used a control group, which may bias their conclusions. Furthermore, these studies had a mean sample size of 55. Seven of 12 studies had samples of less than 30, including several case series. The two largest studies ($N \geq 100$ treated injuries) each retrospectively examined the effects, including complications, associated with injectable therapies for analgesia. In one study of 1,023 local anesthetic injections recorded in a cohort of 100 players, 73% of athletes perceived the therapy as helpful. But, 22% thought

the injury took longer than expected to recover and 6% thought the injury worsened.[54] The other study examined 268 injuries treated with anesthetics (221 injection, 47 topical). Among these, there were 11 minor and 6 major complications.[53]

In addition to the injectable analgesic therapy observational studies, one study examined 28 Australian football players who received intranasal sumatriptan for moderate-to-severe acute headaches (both migraine and non-migraine). The study found that symptoms resolved or became mild in 86% of headaches within two hours of taking sumatriptan.[47] Another qualitative study interviewed 36 breaststroke swimmers about chronic knee pain and concluded that NSAIDs may be useful in reducing symptoms of knee pain.[60]

Studies of attitudes toward pain medications

Four studies assessed elite athletes' knowledge of and attitudes toward pain medication use, either in the broader context of drug use in sports[23, 55, 56] or in the context of playing with injuries.[59] A survey of 446 Finnish athletes on banned substances found that 13.8% of athletes believed narcotic analgesics have performance-enhancing effects; 1.2% said narcotic analgesics had been offered to them, but only 0.5% claimed to know athletes who used these substances.[23] In a series of 11 interviews, elite amateur cyclists described regular use of NSAIDs in combination with caffeine.[55] Pan et al. surveyed collegiate athletes on their attitudes toward 16 banned substances, including morphine. The study found female athletes, more than male athletes, perceived morphine as having some athletic relevance, functional benefits, and some dysfunctional effects.[56] Finally English professional football players, club doctors, and club physiotherapists all described enormous pressures to avoid missing matches due to injury.

They reported injectable analgesic use was related to guilt over missing matches, fear of losing a roster spot, and desire to reach minimum game appearance thresholds to achieve additional pay.[59]

Discussion

We identified and reviewed 70 studies related to pain medications and elite athletes. One important finding was that the majority of the literature describes frequency of pain medication use rather than assessing the effects of pain medications on health-related outcomes. Thus, the majority of the literature directly assessing analgesic use in elite athletes has limited use in directly helping sports healthcare professionals make evidence-based treatment choices relating to pain medications. A second finding was that studies that do assess pain medication efficacy or adverse effects are often several decades old and have unreliable methodologies, including small sample size and lack of control groups, which can contribute to bias in the findings. These weaknesses prevent us from making literature-driven policy or treatment recommendations about pain medication use in elite athletes.

The specific finding with the most empirical support is the widespread use of NSAIDs among elite athletes. Nearly every study that measured use frequency of different pain medications indicated NSAIDs were the most frequently used medication. In football (soccer) in particular, several studies that include data from several international tournaments report in-tournament oral NSAID use among at least 30% of athletes, and in some tournaments more than 50% of athletes. These use rates tend to be much lower than estimates of other pain medication use, including other oral analgesics and injectable NSAIDs, anesthetics, and corticosteroids. These studies do not empirically assess the risks or benefits associated with NSAID use, though studies in general populations and non-elite athletes have identified

health risks related to NSAID use.[14, 85-87] Thus, in the studies we reviewed, the articles' authors frequently question the safety of observed NSAID rates of use. Without specific data, the articles also raise concerns about unsafe patterns of use, such as use of multiple concurrent NSAID use, multiple routes of administration, high dosing, and inappropriate use for pain prophylaxis. Thus, an important area of future study is to develop more rigorous quantitative understanding of the patterns of NSAID use in elite athletes and potential associated health risks.

Varying approaches to estimating analgesic medication use rates made it difficult to make precise comparisons of frequency of use across studies. For example, some studies, such as those relying on doping control data, estimate use based on athlete-reported use in recent days. Other studies survey athletes out of competition and ask about use over longer time periods, such as the past year. Still other studies measured pharmacy dispensing or physician reports of their prescribing of certain medications to elite athletes. Thus, we were unable to make reliable comparisons about use rates, such as over time, across sports, or between different sub-populations of elite athletes. Future research that aims to more reliably compare use rates should consider adopting previously used questionnaires or other measurement methods. We recognize this is challenging when studies often rely on secondary data. Still, future research would benefit from increased consistency in data collection and approaches to measuring and reporting medication use.

A minority of studies reviewed actually examined outcomes of medication use for pain. Furthermore, the literature contains very few RCTs, the most rigorous of research designs. Of the RCTs found, only one was published in the last 25 years. Perhaps owing to challenges of recruiting elite athletes, the RCTs also tended to be conducted on small samples. Thus, we question the generalizability of these results to

today's elite athletes. The observational studies found tended to be published more recently and to focus on the effects of injectable pain medications. These studies' tended to report positively on the effect of injection therapies in having minimal complications, reducing pain, improving function, and helping athletes return to play. However, the validity of these results should be interpreted cautiously due to their tendency to be based on small samples and their lack of control groups. Again, while we recognize practical challenges, future research would benefit from more RCTs and more rigorous retrospective research on pain medications and health outcomes. Such research may benefit from developing or using existing research registries, electronic health record data sources, identifying control groups, and using advanced statistical methods to further control for unobserved differences when comparing athletes who received different treatments.

Our findings suggest some sports and athletes that can be targeted with interventions to prevent analgesic misuse or adverse effects. First, several studies reported relatively high levels of NSAID use among football players,[11, 17, 18, 69, 75, 80] and pressure to use medications to return to play.[59] Therefore, national and international football organizations might consider increasing education and other interventions to mitigate NSAID risks among their constituent athletes. Second, studies reported relatively high analgesic use among collegiate athletes,[8, 38, 64, 74, 82] as well as poor awareness and perceived pressure to use medications.[64, 74, 82] As a result, collegiate and younger athletes generally may also be an important group to better educate about safe analgesic use and effective pain management.

One limitation of this study is that it does not reflect research on pain management in non-elite athletes. However, in this study, we chose a more focused approach that considered elite athletes a distinct group with different needs, pressures, and treatments relative to injury and pain. With this approach, we aimed to summarize evidence that would be most generalizable to elite athletes. A second limitation

of this study is the potential for inaccurate article inclusion or exclusion based on the study population (i.e., elite or non-elite). To mitigate this limitation and apply a consistent identification approach, we used multiple coders and group discussion to resolve disagreement. Also, given our interest in elite athletes, we applied a conservative standard for inclusion, thereby excluding articles for which the population was unclear. Last, we reviewed many studies that varied in their approach to measuring and reporting medication use frequency. As a consequence, our review was unable to quantitatively summarize medication use frequency across studies. Similarly, we found few studies that focused on medication effects and attitudes towards medication use, and many studies we found had small sample sizes. This also limited our ability to quantitatively summarize prior work.

Conclusion

Existing empirical research does not provide a sufficient body of evidence to guide athletes and healthcare professionals in making analgesic medication treatment decisions. Based on the relatively robust evidence regarding the widespread use of NSAIDs, clinicians and policymakers should carefully assess their current recommendations for NSAID use and adhere to a more unified consensus-based strategy for multi-disciplinary pain management in elite athletes. Our hope is that this article and related work will kindle a more rigorous, prospective assessment of various pain management strategies in elite athletes, thus enabling a shift from consensus-based recommendations to evidence-based recommendations.

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Figure Legend

Figure 1: Flow diagram showing process if identifying, screening, assessing eligibility and including final articles for review

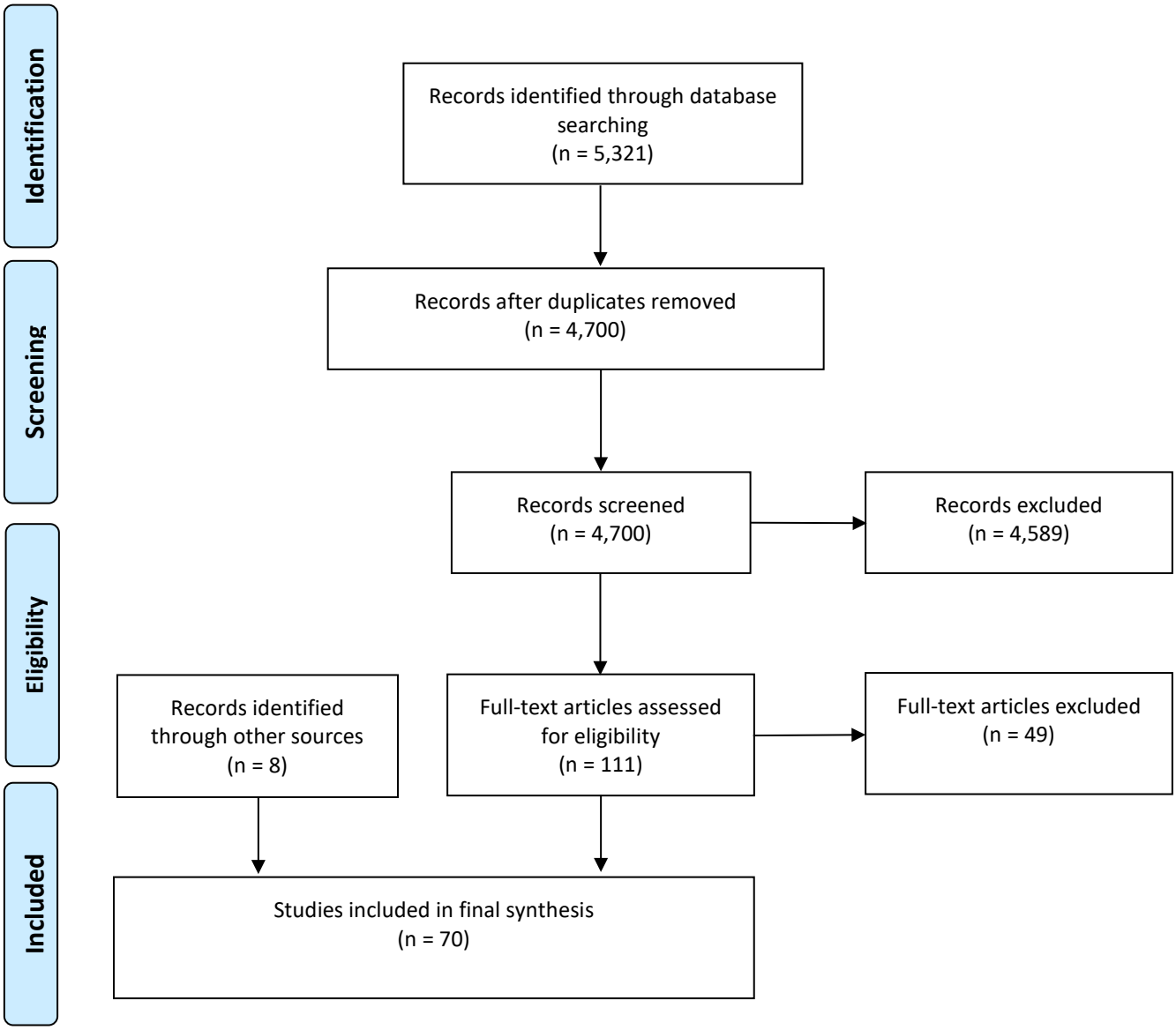

Figure 1: Flow diagram showing process if identifying, screening, assessing eligibility and including final articles for review

Tables

Table 1. Overview of Articles Reporting Oral (or Non-specific Route) NSAID Use Frequency

Article Year	First Author	Title	Sport	Country
1989	Wagner, J.D.	Pharmaceutical services at the Tenth Pan American Games	Multiple	Various
1991	Chan, S.C.	Drug analysis at the 1988 Olympic Winter Games in Calgary	Multiple	Various
2003	Corrigan, B.	Medication use in athletes selected for doping control at the Sydney Olympics (2000)	Multiple	Various
2003	Kujala, U.M.	Use of medications and dietary supplements in later years among male former top-level athletes	Multiple	Finland
2006	Alaranta, A.	Ample use of physician-prescribed medications in Finnish elite athletes	Multiple	Finland
2006	Huang, S.	The use of dietary supplements and medications by Canadian athletes at the Atlanta and Sydney Olympic Games	Multiple	Canada
2007	Taioli, E.	Use of permitted drugs in Italian professional soccer players	Football (Soccer)	Italy
2008	Derman, W.E.	Medication use by Team South Africa during the XXVIIIth Olympiad: A model for quantity estimation for multi-coded team events	Multiple	South Africa
2008	Tscholl P.	The use of medication and nutritional supplements during FIFA World Cups 2002 and 2006	Football (Soccer)	Various
2008	Van Thuyne, W.	Declared use of medication in sports	Multiple	Netherlands, Belgium
2009	Tscholl, P.	The use and abuse of painkillers in international soccer: data from 6 FIFA tournaments for female and youth players	Football (Soccer)	Various
2009	Tsitsimpikou, C.	Medication use by athletes at the Athens 2004 Summer Olympic Games	Multiple	Various
2009	Tsitsimpikou, C.	Medication use by athletes during the Athens 2004 Paralympic Games	Multiple	Various
2010	Tscholl, P.	The use of drugs and nutritional supplements in top-level track and field athletes	Track & Field	Various
2011	Da Silva, E.R.	Non-steroidal anti-inflammatory use in the XV Pan-American Games (2007)	Multiple	Various
2011	Lazic, J.S.	Dietary supplements and medications in elite sport – polypharmacy or real need?	Multiple	Various

2012	de Souza Almeida, F.	Muscle lesion treatment in Brazilian soccer players: Theory vs. Practice	Football (Soccer)	Brazil
2012	Tscholl, P.	Abuse of medication during international football competition in 2010 – lesson not learned	Football (Soccer)	Various
2013	Aavikko, A.	Physician-prescribed medication use by the Finnish Paralympic and Olympic athletes	Multiple	Finland
2013	Holmes, N.	Nonsteroidal anti-inflammatory drug use in collegiate football players	American Football	United States
2014	Loraschi, A.	Dietary supplement and drug use and doping knowledge and attitudes in Italian young elite cyclists	Cycling	Italy
2015	Pedrinelli, A.	Medications and nutritional supplements in athletes during the 2000, 2004, 2008, and 2012 FIFA Futsal World Cups	Football (Soccer)	Various
2015	Tscholl, P.	High prevalence of medication use in professional football tournaments including the World Cups between 2002 and 2014: a narrative review with a focus on NSAIDs	Football (Soccer)	Various
2015	Vaso, M.	Use and abuse of medication during 2014 FIFA World Cup Brazil: a retrospective survey	Football (Soccer)	Various
2015	Yanturali, S.	Injury and illness among athletes during a multi-day elite cycling road race	Cycling	Various

Note: All studies were observational. Data sources included surveys, pharmacy records, laboratory tests, doping control form analyses, and therapeutic use exemption analyses. Specific use rate estimates are not reported due to widely varying methods eliciting and reporting use.

Table 2. Overview of Randomised Controlled Trials of Medication Interventions for Pain

Year	First Author	Title	Sport	Sample Size	Intervention 1	Intervention 2	Outcome(s)
1975	Muckle, D.S.	Section 1 ibuprofen ('Brufen') in soft-tissue injuries	Football (soccer)	60	NSAID oral: ibuprofen	NSAID oral: aspirin	Pain, Return to sport
1976	Muckle, D.S.	A comparative study of flurbiprofen and aspirin in soft tissue trauma	Football (soccer)	52	NSAID oral: flurbiprofen	NSAID oral: aspirin	Pain, Return to sport
1980	Santilli, G.	Comparative study with piroxicam and ibuprofen versus placebo in the supportive treatment of minor sports injuries	Multiple	30	NSAID oral: piroxicam	NSAID oral: ibuprofen	Pain, Function
1984	Surbey, G.D.	Effects of naloxone on exercise performance	Track (middle distance)	13	Naloxone	Placebo	Vitals (O2 uptake, heart rate, ventilation), Perceived exertion, Pain perception
1986	Indelicato, P.A.	Comparison of diflunisal and acetaminophen with codeine in the treatment of mild to moderate pain due to strains and sprains	American Football	50	NSAID oral: diflunisal	Other analgesic: Paracetamol and codeine	Pain, Musculoskeletal swelling
1988	McIlwain, H.H.	Piroxicam versus naproxen in the treatment of acute musculoskeletal disorders in athletes	Multiple	34	NSAID oral: piroxicam	NSAID oral: naproxen	Pain, Musculoskeletal damage/deformity

1990	Galasso, G.	Analgesic activity of beta-cyclodextrin-piroxicam and tenoxicam in acute soft tissue injuries	Football (soccer)	49	NSAID oral: Piroxicam	NSAID oral: tenoxicam	Prevalence of pain
2006	Hoksrud, A.	Ultrasound-guided sclerosis of neovessels in painful chronic patellar tendinopathy: a randomized controlled trial	Multiple	43	Polidocanol injection	Lidocaine/epinephrine injection	Pain, Function

Table 3. Overview of Observation Studies of Medication Interventions for Pain

Year	First Author	Title	Sport	Sample Size	Intervention	Outcome(s)
1985	Rovere, G.D.	Frequency, associated factors, and treatment of breaststroker's knee in competitive swimmers	Swimming	36	NSAID	Pain
1995	Holt, M.A.	Treatment of osteitis pubis in athletes. Results of corticosteroid injections	Multiple	12	Corticosteroid injection	Return to sport
2000	Levine, W.N.	Intramuscular corticosteroid injection for hamstring injuries. A 13-year experience in the National Football League	American football	58	Corticosteroid injection	Complications, Return to sport
2002	Orchard, J.W.	Benefits and risks of using local anaesthetic for pain relief to allow early return to play in professional football	Multiple	268	Local anaesthetic injection or topical	Complications
2002	O'Connell, M.J.	Symphyseal cleft injection in the diagnosis and treatment of osteitis pubis in athletes	Multiple	16	Local anaesthetic and steroid injection	Pain, Return to sport
2005	McCrory, P.	Open label study of intranasal sumatriptan (Imigran) for footballer's headache	Football (soccer)	38	intranasal sumatriptan	Pain
2005	Alfredson, H.	Neovascularisation in chronic painful patellar tendinosis-promising results after sclerosing neovessels outside the tendon challenge the need for surgery	Multiple	15	sclerosing injection	Pain
2005	Topol, G.A.	Efficacy of dextrose prolotherapy in elite male kicking-sport athletes with chronic groin pain	Multiple	24	Dextrose injection	Pain, Function
2005	Szalai, K.	Sacral epidural steroid injections used for the prevention of hamstring injuries	Multiple	25	Epidural steroid injection	Pain Recovery time
2007	Schilders, E.	Adductor-related groin pain in competitive athletes. Role of adductor enthesis, magnetic resonance imaging, and entheseal pubic cleft injections	Multiple	24	Local anaesthetic and steroid injection	Pain, Recurrence
2008	Topol, G.A.	Regenerative injection of elite athletes with career-altering chronic groin pain who fail conservative treatment: A consecutive case series	Multiple	72	Dextrose injection	Pain, Return to sport
2008	Hoksrud, A.	Color doppler ultrasound findings in patellar tendinopathy (jumper's knee)	Multiple	63	sclerosing injection	Function
2010	Orchard, J.W.	Long-term safety of using local anesthetic injections in professional rugby league	Rugby	100	Local anaesthetic injection	Satisfaction;, Complications
2012	Krych, A.J.	Epidural steroid injection for lumbar disc herniation in NFL athletes	American football	17	Epidural steroid injection	Return to sport

Appendix. Detailed Search Strategy

Database	Search
OVID	1. olympi*.mp. 2. compet*.mp. 3. premier.mp. 4. 'high level'.mp. 5. colleg*.mp. 6. professional*.mp. 7. "major league".mp. 8. "elite".mp. 9. "top-level".mp. 10. "world-class".mp. 11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 12. athlet*.mp. 13. exp sports medicine/ 14. exp sport/ 15. exp exercise/ 16. exp athletic injuries/ 17. sport*.mp. 18. player*.mp. 19. 12 or 13 or 14 or 15 or 16 or 17 or 18 20. exp analgesics/ 21. nsaid*.mp. 22. opioid*.mp. 23. exp acetaminophen/ 24. exp aspirin/ 25. exp "Anesthesia and Analgesia"/ 26. exp Anti-Inflammatory Agents/ 27. exp narcotics/ 28. exp pain/ 29. exp pain management/ 30. exp prescription drug misuse/ 31. (Alfentanil or Alphaprodine or Buprenorphine or Butorphanol or Codeine or Dextromoramide or Dextropropoxyphene or Dihydromorphine or Diphenoxylate or Enkephalin Ala 2-MePhe 4-Gly 5 or Enkephalin, D-Penicillamine 2,5 or Ethylketocyclazocine or Ethylmorphine or Etorphine or Fentanyl or Heroin or Hydrocodone or Hydromorphone or Levorphanol or Meperidine or Meptazinol or Methadone or Methadyl Acetate or Morphine or Nalbuphine or Opiate Alkaloid$ or Opium or Oxycodone or Oxymorphone or Pentazocine or Phenazocine or Phenoperidine or Pirinitramide or Promedol or Sufentanil or Tilidine or Tramadol or pethidine or dihydrocodeine).mp.

	32. (4,5-Dihydro-1-3-trifluoromethyl phenyl 1H-pyrazol-3-amine or Ampyrone or Antipyrine or Apazone or Aspirin or Bufexamac or Clonixin or Curcumin or Diclofenac or Diflunisal or Dipyrone or Epirizole or Fenoprofen or Feprazone or Flurbiprofen or Ibuprofen or Indomethacin or Ketoprofen or Ketorolac or Ketorolac Tromethamine or Meclofenamic Acid or Mefenamic Acid or Mesalamine or Naproxen or Niflumic Acid or Oxyphenbutazone or Phenylbutazone or Piroxicam or Salicylates or Sodium Salicylate or Sulfasalazine or Sulindac or Suprofen or Tolmetin).mp. 33. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 34. 11 and 19 and 33 35. limit 34 to (english language and humans)
CINHAL	1. olympi* OR compet* OR premier OR "high level" OR colleg* OR professional* OR "major league" OR elite OR "top-level" OR "world-class" 2. (sport* or player*) or MH athletes or MH "sports medicine" or MH SPORTS 3. "ANALGESICS" OR "ACETAMINOPHEN" OR "ANTIPYRETICS" OR "CLONIDINE" OR "DIMETHYL sulfoxide" OR "FLURBIPROFEN" OR "IBUPROFEN" OR "OXYCODONE" 4. "NONSTEROIDAL anti-inflammatory agents" OR "ASPIRIN" OR "FLURBIPROFEN" OR "IBUPROFEN" OR "INDOMETHACIN" OR "KETOROLAC (Drug)" OR "NAPROXEN" OR "PHENYLBUTAZONE" OR "PIROXICAM" 5. "ANESTHESIA" OR "CONDUCTION anesthesia" 6. "ANALGESIA" OR "TRANSCUTANEOUS electrical nerve stimulation" 7. MH "ANTI-inflammatory agents" OR MH "DICLOFENAC" OR MH "DIMETHYL sulfoxide" OR MH "GLUCOCORTICOIDS" OR MH "NONSTEROIDAL anti-inflammatory agents" 8. MH "NARCOTICS" OR MH "COCAINE" OR MH "HASHISH" OR MH "HEROIN" OR MH "MORPHINE" OR MH "OXYCODONE" 9. MH "PAIN" OR "ABDOMINAL pain" OR "BACKACHE" OR "CENTRAL pain" OR "CHEST pain" OR "CHRONIC pain" OR "COMPLEX regional pain syndromes" OR "EARACHE" OR "ELBOW pain" OR "FACIAL pain" OR "FOOT pain" OR "GROIN pain" OR "HEADACHE" OR "INTRACTABLE pain" OR "KNEE pain" OR "LEG pain" OR "MYALGIA" OR "MYOFASCIAL pain syndromes" OR "NECK pain" OR "PAIN management" OR "PAIN measurement" OR "PELVIC pain" OR "SHOULDER pain" OR "SIDE stitch"

	10. "nsaid*" OR "opioid*" OR ((Alfentanil or Alphaprodine or Buprenorphine or Butorphanol or Codeine or Dextromoramide or Dextropropoxyphene or Dihydromorphine or Diphenoxylate or Enkephalin Ala 2-MePhe 4-Gly 5 or Enkephalin, D-Penicillamine 2,5 or Ethylketocyclazocine or Ethylmorphine or Etorphine or Fentanyl or Heroin or Hydrocodone or Hydromorphone or Levorphanol or Meperidine or Meptazinol or Methadone or Methadyl Acetate or Morphine or Nalbuphine or Opiate Alkaloid$ or Opium or Oxycodone or Oxymorphone or Pentazocine or Phenazocine or Phenoperidine or Pirinitramide or Promedol or Sufentanil or Tilidine or Tramadol or pethidine or dihydrocodeine)) OR ((4,5-Dihydro-1-3-trifluoromethyl phenyl 1H-pyrazol-3-amine or Ampyrone or Antipyrine or Apazone or Aspirin or Bufexamac or Clonixin or Curcumin or Diclofenac or Diflunisal or Dipyrone or Epirizole or Fenoprofen or Feprazone or Flurbiprofen or Ibuprofen or Indomethacin or Ketoprofen or Ketorolac or Ketorolac Tromethamine or Meclofenamic Acid or Mefenamic Acid or Mesalamine or Naproxen or Niflumic Acid or Oxyphenbutazone or Phenylbutazone or Piroxicam or Salicylates or Sodium Salicylate or Sulfasalazine or Sulindac or Suprofen or Tolmetin)) 11. S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 12. S1 AND S2 AND S11 13. Academic Journals
SportDISCUS	1. SU "OLYMPIC athletes" OR SU "WOMEN Olympic athletes" OR SU "ELITE athletes" OR SU "PROFESSIONAL athletes" OR SU "AFRICAN American professional athletes" OR SU "FREE agents (Sports)" OR SU "LGBT professional athletes" OR SU "WOMEN professional athletes" OR SU "COLLEGE athletes" OR SU "COLLEGE basketball players" OR SU "COLLEGE football players" OR SU "COMMUNITY college athletes" OR SU "MALE college athletes" OR SU "SEXUAL minority college athletes" OR SU "WOMEN college athletes" 2. olympi* OR compet* OR premier OR "high level" OR colleg* OR professional* OR "major league" OR elite OR "top-level" OR "world-class" 3. S1 OR S2 4. "ANALGESICS" OR "ACETAMINOPHEN" OR "ANTIPYRETICS" OR "CLONIDINE" OR "DIMETHYL sulfoxide" OR "FLURBIPROFEN" OR "IBUPROFEN" OR "OXYCODONE" 5. "NONSTEROIDAL anti-inflammatory agents" OR "ASPIRIN" OR "FLURBIPROFEN" OR "IBUPROFEN" OR

	"INDOMETHACIN" OR "KETOROLAC (Drug)" OR "NAPROXEN" OR "PHENYLBUTAZONE" OR "PIROXICAM" 6. "OPIOIDS" OR "OXYCODONE" 7. "ANESTHESIA" OR "CONDUCTION anesthesia" 8. "ANALGESIA" OR "TRANSCUTANEOUS electrical nerve stimulation" 9. "nsaid*" OR "opioid*" OR ((Alfentanil or Alphaprodine or Buprenorphine or Butorphanol or Codeine or Dextromoramide or Dextropropoxyphene or Dihydromorphine or Diphenoxylate or Enkephalin Ala 2-MePhe 4-Gly 5 or Enkephalin, D-Penicillamine 2,5 or Ethylketocyclazocine or Ethylmorphine or Etorphine or Fentanyl or Heroin or Hydrocodone or Hydromorphone or Levorphanol or Meperidine or Meptazinol or Methadone or Methadyl Acetate or Morphine or Nalbuphine or Opiate Alkaloid$ or Opium or Oxycodone or Oxymorphone or Pentazocine or Phenazocine or Phenoperidine or Pirinitramide or Promedol or Sufentanil or Tilidine or Tramadol or pethidine or dihydrocodeine)) OR ((4,5-Dihydro-1-3-trifluoromethyl phenyl 1H-pyrazol-3-amine or Ampyrone or Antipyrine or Apazone or Aspirin or Bufexamac or Clonixin or Curcumin or Diclofenac or Diflunisal or Dipyrone or Epirizole or Fenoprofen or Feprazone or Flurbiprofen or Ibuprofen or Indomethacin or Ketoprofen or Ketorolac or Ketorolac Tromethamine or Meclofenamic Acid or Mefenamic Acid or Mesalamine or Naproxen or Niflumic Acid or Oxyphenbutazone or Phenylbutazone or Piroxicam or Salicylates or Sodium Salicylate or Sulfasalazine or Sulindac or Suprofen or Tolmetin)) 10. S4 OR S5 OR S6 OR S7 OR S8 OR S9 11. S3 AND S10 12. Academic journals
Embase	1. 'athlete'/exp OR athlete.tw OR 'sports medicine'/exp OR 'sports medicine.tw' OR 'sport'/exp OR sport.tw OR player*.tw 2. 'olympic team' OR 'olympics' OR 'olympia' OR compet*.tw OR premier OR 'high-level' OR colleg*.tw OR professional*.tw OR 'major league' OR elite OR 'top-level' OR 'world-class' 3. 'analgesic'/exp OR 'narcotic agent'/exp OR 'anesthesia'/exp OR 'anti inflammatory agent'/exp OR 'narcotic analgesic'/exp OR 'pain'/exp OR 'opioid'/exp OR 'nonsteroidal antiinflammatory agent'/exp 4. alfentanil OR alphaprodine OR buprenorphine OR butorphanol OR codeine OR dextromoramide OR dextropropoxyphene OR dihydromorphine OR

	diphenoxylate OR 'enkephalin ala 2-mephe 4-gly 5' OR 'enkephalin, d-penicillamine 2,5' OR ethylketocyclazocine OR ethylmorphine OR etorphine OR fentanyl OR heroin OR hydrocodone OR hydromorphone OR levorphanol OR meperidine OR meptazinol OR methadone OR 'methadyl acetate' OR morphine OR nalbuphine OR 'opiate alkaloid' OR opium OR oxycodone OR oxymorphone OR pentazocine OR phenazocine OR phenoperidine OR pirinitramide OR promedol OR sufentanil OR tilidine OR tramadol OR pethidine OR dihydrocodeine OR '4,5-dihydro-1-3-trifluoromethyl phenyl 1h-pyrazol-3-amine' OR ampyrone OR antipyrine OR apazone OR aspirin OR bufexamac OR clonixin OR curcumin OR diclofenac OR diflunisal OR dipyrone OR epirizole OR fenoprofen OR feprazone OR flurbiprofen OR ibuprofen OR indomethacin OR ketoprofen OR ketorolac OR 'ketorolac tromethamine' OR 'meclofenamic acid' OR 'mefenamic acid' OR mesalamine OR naproxen OR 'niflumic acid' OR oxyphenbutazone OR phenylbutazone OR piroxicam OR salicylates OR 'sodium salicylate' OR sulfasalazine OR sulindac OR suprofen OR tolmetin 5. (1 AND 2 AND (3 OR 4))AND [humans]/lim AND [english]/lim
Cochrane	1. MeSH descriptor: [Analgesics] explode all trees 2. MeSH descriptor: [Acetaminophen] explode all trees 3. MeSH descriptor: [Aspirin] explode all trees 4. MeSH descriptor: [Anesthesia and Analgesia] explode all trees 5. MeSH descriptor: [Anti-Inflammatory Agents] explode all trees 6. MeSH descriptor: [Narcotics] explode all trees 7. MeSH descriptor: [Pain] explode all trees 8. MeSH descriptor: [Pain Management] explode all trees 9. NSAID* 10. opioid* 11. (alfentanil or alphaprodine or buprenorphine or butorphanol or codeine or dextromoramide or dextropropoxyphene or dihydromorphine or diphenoxylate or "Enkephalin Ala 2-MePhe 4-Gly 5" or "Enkephalin, D-Penicillamine 2,5" or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or levorphanol or meperidine or meptazinol or methadone or Methadyl Acetate or morphine or nalbuphine or Opiate Alkaloid or

	opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or tilidine or tramadol or pethidine or dihydrocodeine or "4,5-Dihydro-1-3-trifluoromethyl phenyl 1H-pyrazol-3-amine" or ampyrone or antipyrine or apazone or aspirin or bufexamac or clonixin or curcumin or diclofenac or diflunisal or dipyrone or epirizole or fenoprofen or feprazone or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or "Ketorolac Tromethamine" or Meclofenamic Acid or "Mefenamic Acid" or mesalamine or naproxen or "Niflumic Acid" or oxyphenbutazone or phenylbutazone or piroxicam or salicylates or Sodium Salicylate or sulfasalazine or sulindac or suprofen or tolmetin) 12. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 13. MeSH descriptor: [Athletes] explode all trees 14. MeSH descriptor: [Sports Medicine] explode all trees 15. MeSH descriptor: [Sports] explode all trees 16. MeSH descriptor: [Athletic Injuries] explode all trees 17. player* 18. (#13 or #14 or #15 or #16 or #17) 19. olympi* or compet* or premier or "high-level" or colleg* or professional* or "major-league" or elite or "top-level" or "world-class":ti,ab,kw (Word variations have been searched) 20. #12 and #18 and #19
Scopus	(TITLE-ABS-KEY (olympi* OR compet* OR premier OR {high level} OR colleg* OR professional* OR {major league} OR elite OR {top-level} OR {world-class})) AND (TITLE-ABS-KEY (athlet* OR "sports medicine" OR sport OR "athletic injuries" OR player*)) AND (ALL (alfentanil OR alphaprodine OR buprenorphine OR butorphanol OR codeine OR dextromoramide OR dextropropoxyphene OR dihydromorphine OR diphenoxylate OR "Enkephalin Ala 2-MePhe 4-Gly 5" OR "Enkephalin, D-Penicillamine 2,5" OR ethylketocyclazocine OR ethylmorphine OR etorphine OR fentanyl OR heroin OR hydrocodone OR hydromorphone OR levorphanol OR meperidine OR meptazinol OR methadone OR "Methadyl Acetate" OR morphine OR nalbuphine OR "Opiate Alkaloid*"

	OR opium OR oxycodone OR oxymorphone OR pentazocine OR phenazocine OR phenoperidine OR pirinitramide OR promedol OR sufentanil OR tilidine OR tramadol OR pethidine OR dihydrocodeine OR "4,5-Dihydro-1-3-trifluoromethyl phenyl 1H-pyrazol-3-amine" OR ampyrone OR antipyrine OR apazone OR aspirin OR bufexamac OR clonixin OR curcumin OR diclofenac OR diflunisal OR dipyrone OR epirizole OR fenoprofen OR feprazone OR flurbiprofen OR ibuprofen OR indomethacin OR ketoprofen OR ketorolac OR "Ketorolac Tromethamine" OR "Meclofenamic Acid" OR "Mefenamic Acid" OR mesalamine OR naproxen OR "Niflumic Acid" OR oxyphenbutazone OR phenylbutazone OR piroxicam OR salicylates OR "Sodium Salicylate" OR sulfasalazine OR sulindac OR suprofen OR tolmetin OR analgesics OR acetaminophen OR aspirin OR anesthesia AND analgesia OR anti-inflammatory AND agents OR narcotics OR pain OR nsaid OR opioid*)) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (EXACTKEYWORD , "Human") OR LIMIT-TO (EXACTKEYWORD , "Humans"))