A Narrative Review: The Use of the Topical NSAID Ibuprofen for the Treatment of Knee Osteoarthritis. Supporting Clinician Decision-Making in the First-Line Treatment of Osteoarthritis

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ABSTRACT

A NARRATIVE REVIEW: The use of the topical nonsteroidal anti-inflammatory drugs (NSAID) ibuprofen for the treatment of knee osteoarthritis. Supporting clinician decision-making in the first-line treatment of osteoarthritis.

OBJECTIVE: To open discussion at a clinical level on the guidelines for the pharmacological management of osteoarthritis of the knee, this narrative review looks into the use of topical NSAID being a clinically effective, safe, and cost-efficient treatment compared to an oral alternative.

BACKGROUND: With the over prescription of NSAIDs in the age of above 65 years, there has been a call for increased restrictions of the sale of oral preparations of NSAIDs. It is our view that there is still a lack of awareness in the benefit of topical NSAIDs to the patient (no evidence of adverse reactions recorded by the Joint Formulary Committee [JFC] to date) as well as provider (topical application is cheaper as a National Health Service [NHS] prescription).

METHODS: Key online resources included PubMed, Athens, Cochrane Library, Google Scholar, MEDLINE, and relevant clinical and commissioning guidelines with the final date of data collection in March 2017. We also contacted the manufacturer and license holder directly for further clarification. Randomized, double-blind control studies, commissioned reports, International Guidelines, MEHA Guidelines, and license holder data were included. Where possible studies included had to have fair randomization and adhere to key treatment pathways as highlighted by National Institute for Health and Clinical Excellence (NICE) and other guidelines.

DISCUSSION: Current guidelines advise that patients who seek initial treatment of osteoarthritis of the knee should consider a combination of treatment modalities, including pharmacological therapies, particularly the use of NSAIDs. At a clinical level, a reoccurring issue identified with this advice is the inappropriate use of oral NSAIDs, and the concern that the risks associated with ease of access ("over the counter"), and overuse, may result in systemic adverse events in this cohort of patients. Multiple studies have examined the negative effect of oral NSAIDs and the associated risks of use. We were unable to source studies that showed any adverse systemic events from the use of topical NSAIDs; however, there are good quality trials comparing oral to topical NSAIDs, showing similar levels of efficacy at 6 and 12 weeks.

CONCLUSION: Topical NSAIDs provide good levels of pain relief in subjects with mild to moderate knee osteoarthritis. There is also evidence for the use of the topical application being a clinically effective, safe, and cost-efficient treatment.

KEYWORDS: Knee osteoarthritis, osteoarthritis, drug administration, topical, topical administration, agents, nonsteroidal anti-inflammatory drugs, analgesics, anti-inflammatory, inappropriate prescribing

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Introduction

There are many challenges facing the National Health Service (NHS) as more of the population are living with long-term conditions, and at the same time, our budgets are under increasing pressure. As clinicians, we have a responsibility in developing and maintaining standardized evidence-based approach to patient care. Current guidelines set by National Institute of Clinical Excellence (NICE)[1] and expanded by the European Society for Clinical and Economic Aspect of Osteoporosis and Osteoarthritis (ESCEO)[2] advise that in patients with symptomatic arthritis of the knee(s), the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is a good treatment option. Most recently, they have become more widely available, cheap, and available without prescription, subsequently presenting us with a medication that is at risk of overuse, leading health care providers to demand as safe a preparation as possible.

The prevalence of hip and knee disease is at its highest among those who are 65 years and above 65 years.[1,3] Due to a good level of evidence for the efficacy of topical NSAIDs in chronic musculoskeletal (MSK) pain, ibuprofen was the most popular and commonly used NSAID for this age group.[3] Although we found no current literature to support this hypothesis, one could theorize that this is partly due to its availability as an "over-the-counter" medication, as well as the

advertiser influence of its beneficial qualities for MSK pain. As a prescribing service, it is also a cheaper option in its nonproprietary formulation (nonbranded).

A recent review[4] highlighted only a few recent studies that compared oral NSAIDs to topical application, and although at that time they were weary of the benefits of long-term topical NSAIDs, their final recommendation was to support its use for patients who might not tolerate oral NSAIDs. Since then, a recent Cochrane systematic review[5] highlights additional studies that are of a better quality and have the potential to support a shift in perception of the increased benefits of topical application compared to oral administration of this drug. This advice is also supported by multiple international guidelines (see Table 1) mainly due to their safety record with adverse events.

This narrative review was undertaken to support changes in prescribing practice for a better cohesion of care through appropriate prescribing, with the gold standard for the treatment of arthritis (in its early pre-surgical stages) requiring a co-dependent combination of pharmacological and nonpharmacological interventions.[1,2] We, as clinicians, need to make informed choices, so that medication supplied to our patients is correct and properly dispensed.

Review of the Literature

Situation

The initial search looked for studies that used topical NSAIDs for those in chronic pain of the knees caused by mild to moderate osteoarthritis (OA) and subsequently treated with topical ibuprofen, as well as studies on the associated risks of long-term use. Many of these studies highlighted one of the disabling factors of OA as a condition being pain as a direct result of the inflammatory process.[10]

Mechanism of action

During this inflammatory pathway, arachidonic acid is metabolized in 2 pathways, with subsequent potentiate effect on histamine, resulting in an increased vessel wall permeability and sensitization of the nociceptor peripheral terminals of afferent neurons residing the pain thresholds.[11] The clinical efficacy of ibuprofen has the capacity for prostanoid inhibition, limiting the subsequent potentiate of histamine and bradykinines, thus limiting the nociceptive clinical presentation of swelling and pain. In their 2010 study, Tiso et al[12] discussed how Ibuprofen reversibly binds to only one of the monometer, and lead source of prostaglandin formation, of the Cox dimers (COX2), to stop the formation of the prostanoid.

Although weaker than some other NSAIDs (ie, Diclofenac), we found that current practice[13] supports ibuprofen as a drug of choice due to its beneficial analgesic and antipyretic effect. In their recent review[14] of the pharmacological and pharmokinetic effects of NSAIDs, Bushra and Aslam found ibuprofen to be as effective as diclofenac in the treatment of this condition with less associated risks, such as the risk of hematemesis, ulcers (peptic), and gastric pain/vomiting in chronic users. This supports its selection as a good pharmacological choice for the treatment of knee arthritis. Furthermore, McPherson and Cimino[15] concluded that the inclusion of NSAIDs alongside nonopioid analgesia could lead to a better analgesic cover than a low-potency opioid such as codeine.

Prescription

Ibuprofen topical gel can be found in the British National Formulary (BNF) as nonproprietary 5% and 10% in 30 g, 50 g, and 100 g tubes.[16] Although all patients' information literature (PIL) for the 5% and 10% formula found online via the EMC[16-18] advises against using more than the recommended dose in a 24-hour period, there is no documented evidence to support this, with no current reported overdoses of topical NSAIDs.[13] Interestingly, the patient advice leaflets for the 5% gel have no advice on amount or size of each dose, although they do advise a maximum application of 4 times a day. The 10% formulation dosage is 2 to 5 cm of gel (50-125 mg ibuprofen) used up to 4 times daily, with individual doses administered at least 4 hours apart, with "patients should not apply more than 500 mg of ibuprofen (5 g gel) in any 24 hour period."[17,18] Direct discussion with the UK license holder AMCo Medical Information failed to clarify any further their dosage advice or evidence to support this.

Bioavailability and effectiveness

Topical compared to oral administration bypasses the first (pass) liver metabolism, thus allowing for a higher plasma concentration of the drug without increasing the dose, offering an increased efficacy of the drug as it causes a great local action at the site of inflammation, without greater systemic exposure.[19] Penetrating the skin barrier is a key-limiting factor to the use of topical ibuprofen as a drug,[19] partly due to its lipophilic property of being almost insoluble in water, having a pKA of 5.3.[14] Absorption may also be affected by a number of factors including age, temperature, and ethnicity.[4] Clinical (drug company) experiments with dermis layers suggest that a cream application has a less effective penetration than gel and to compensate for this, it is often formulated with propan 2-ol, which is of medium polarity, improving its percutaneous penetration (prescription of cream preparation is not allowed in the United Kingdom,[13] and we have therefore not reviewed this preparation further). This combination is of sufficient polarity to carry the ibuprofen through the skin, but not so polar that it will not allow dissolution of the drugs through the skin. This formulation penetrated through the skin at approximately 22% of a finite dose within 48 hours,[20] achieving a therapeutically relevant local concentration in underlying tissue, joints, and the synovial fluid in a relatively short time,[19] with local synovium and plasma levels, at the site of application being on par with oral ibuprofen.

Table 1. International guidelines for osteoarthritis.

TITLE	ACCESSED	DATE	CONTENT
American Academy of Orthopaedic Surgeons. *Treatment of Osteoarthritis of the Knee (Non-Arthroplasty): Full Guideline*. Rosemont, IL:[6]	American *Academy of Orthopaedic Surgeons; http://www.aaos.org/research/guidelines/oakguideline.pdf*	2013	An updated systematic review of current research. This guideline contains 15 recommendations
American Geriatrics Society (AGS) Panel on the Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons[7]	*J Am Geriatr Soc. 2009;57*(8):*1331-1346. http://www.americangeriatrics.org/files/documents/2009_Guideline.pdf.*	2009	Updating the evidence base of the 2002 guidelines providing recommendations regarding the use of pharmacological approaches in the management of persistent pain in the older population.
Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Bruyere O, Cooper C, Pelletier J-P, Branco J, Brandi ML, et al. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: A report from a task force of the European Society for Clinical and ESCEO[2]	*Semin Arthritis 2014;*44:253-236	2014	Following the published guidelines, this developed algorithm prioritized the interventions for osteoarthritis of the knee in a given sequence to support clinicians decision making for the management of this condition
Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee[8]	*Arthritis Care Res. 2012;64*(4):*465-474. http://www.rheumatology.org/practice/clinical/guidelines/PDFs/ACR_OA_Guidelines_FINAL.pdf. Accessed 23/3/2017.*	2012	A systemic review of the pharmacologic and nonpharmacologic modalities used to manage knee, hip, and hand OA. Clinical scenarios were generated to represent patients with symptomatic hip, knee, and hand OA
Jordan KM, Arden NK, Doherty M. et al EULAR Recommendations: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT) [extended report].[9]	*Ann Rheum Dis. 2003;62*(12):*1145-1155. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1754382/pdf/v062p01145.pdf. Accessed 05/1/17.*	2003	EULAR literature search and updated guidelines, recommending the management of OA knee. This was restricted to treatments for knee OA with clinical and/or radiological OA of any compartment of the knee.
National Institute for Health and Clinical Excellence. *Osteoarthritis: The Care and Management of Osteoarthritis in Adults*.[1]	NICE Clinical Guideline 59. London, England: *National Institute for Health and Clinical Excellence*	2008 Updated 2014	Best practice in the assessment and management of osteoarthritis in adults. Covering both pharmacological and nonpharmacological treatments. Promoting effective treatment options to control pain and improve function
Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines.[10]	*Osteoarthritis Cartilage.* 2008;*16*(2):137-162. *http://www.oarsi.org/pdfs/oarsi_recommendations_for_management_of_hip_and_knee_oa.pdf. Accessed 10/12/16*	2008	A concise, patient-focussed, evidence-based, consensus with recommendations to support clinicians in the management of hip and knee osteoarthritis (OA)

Abbreviations: EULAR, European League Against Rheumatism; NICE, National Institute for Health and Clinical Excellence.

Adverse reactions

Current studies show that the topical application side effects mainly centre on the photosensitivity of the gel, as well as the risk of local skin reactions of rashes and itching.[5] Although topical application has a low risk of adverse effects compared to oral, partly due to its plasma levels being less than 5% compared to an oral administration,[21] as of yet we are uncertain of its effect on platelet function,[20] renal impairment, or cardiac events.[3]

Method

Objectives

Through a review of literature from randomized controlled studies, commissioned reports, international guidelines, MRHA guidelines, and licence holder data, we aimed to support colleagues to consider changing their prescribing practice. Through reviewing the safety and efficacy of topical ibuprofen, and providing supportive literature, we aimed to ensure a more appropriate topical preparation for the treatment of mild to moderate knee OA.

Report of project

After an initial broad search of key words (see Table 2) chosen resulted in 111 studies, 31 were discounted by title and 24 by abstract. Finally, one cohort study,[3] a randomized unblinded pilot study,[12] a randomized controlled double-blind study,[11] and a double-blind, double-dummy randomized control study[19] were included in this review as they represented the

higher classification of studies available. Searches were also compiled through the reference list of 4 key literature reviews[4,5,14,15] although their articles not included in this study fell outside of our time line parameters and therefore were not included individually in this review (see Table 3). Due to the limited current literature, we also included the MRHA scientific discussion for 5% and 10% preparation,[20,21] NICE guidelines,[1] and correspondence with the UK licence holders for further guidance.[17,18]

Studies selected included adult participants only, who complained of chronic knee pain for a minimum of 3 months, with radiological confirmation of disease. Studies not selected included acute knee pain or those that had nonosteoarthritis causes for their chronic MSK pain. Of the selected studies, the main treatment modality was topical NSAID, with a comparison of either placebo or oral preparation. As this literature review was to support an evidence-based learning, and a change in prescribing practice, studies that reviewed the inflammatory process of OA and the effects of NSAIDs on inflammation were also included.

Through the process of elimination, a final cohort of studies was selected. Three key articles compared topical NSAIDs with at least one other modality be that placebo[19] oral[12] or both.[11] Although all studies aimed for a final outcome of improvement, assessment criteria did differ; these included pain, range, and function (Western Ontario and McMaster Universities Arthritis Index [WOMAC]) with a varying timeframe of 6 to 12 weeks. Key inclusion criteria for all 3 studies included male and female participants and diagnosis of OA via clinical and radiological examinations, with a mean age range of 40 to 85 years. Exclusion criteria included pregnancy, nonosteoarthritic cause for knee pain, or skin disease.

Although the most common topical preparation in the United Kingdom is ibuprofen[3] mainly due to its reduced cost and increased safety record compared to others (ie, diclofenac), there is a very small number of studies specifically on this NSAID. As the action of ibuprofen on the inflammatory pathway is inherently the same as diclofenac,[14] and diclofenac is the drug of choice for the US market, we included studies of this topical and oral preparation of NSAID.

Instructions for use in all studies followed the MRHA,[20,21] JFC,[13] and NICE[1] guidelines of application. For further guidance on research for this, we directly contacted the licence holder company, as per their reply there is as yet no evidence to support quantity or frequency of application. All studies included were clear on application, although no finite dose was given and amount and frequency were clearly described.

Two studies compared 2 types of topical application with an oral version, with an outcome of comparative symptom improvement between topical and oral.[11,19] These double-blind, randomized control studies included a mixed cohort of male and female participants, with a mean age of 40 to 85 years. Although only the study by Baer et al[11] went as far as 6 weeks of treatment, Simon et al[19] took this further to 12 weeks. Clinically, 12 weeks do count as a chronic presentation; however, as the age of developing arthritis can vary from 30 to 80 years, a maximum of 12-week window of review is nominal in comparison. Both these studies were found to be of high quality when using the Oxford quality score,[22] this was due to their

Table 2. MeSH key search words.

KNEE OSTEOARTHRITIS	OSTEOARTHRITIS
Drug administration	Topical
Topical administration, agents	Nonsteroidal anti-inflammatory, analgesics
Anti-inflammatory	Inappropriate prescribing

Table 3. inclusion/exclusion criteria.

INCLUSION CRITERIA	EXCLUSION CRITERIA
Participants above 18 years (mean age range 40-85 years)	Acute knee pain
Chronic knee pain for a minimum of 3 months	Nonosteoarthritis cause for knee pain
Topical NSAID as treatment modality	Pregnant
Comparison with oral or placebo treatment	Skin disease
Review of inflammatory process	Under 18 years of age
Effect of NSAID on inflammation	Not including topical NSAID
Male and female participants	Not comparing with oral or placebo treatment
Radiological diagnosis of OA	Does not include a review of inflammatory process
Clinical diagnosis of OA: pain, crepitus, early morning stiffness, stiffness post increased activity	No clinical diagnosis of OA: pain, crepitus, early morning stiffness, stiffness post increased activity
	No radiological diagnosis of OA

Abbreviations: NSAID, Nonsteroidal Anti-Inflammatory Drugs; OA, osteoarthritis.

random allocation into treatment groups, and either blind or double blinded, reducing the risk of bias. However, these represented the minority within the studies found on this topic within our elected time frame (2005 to 2016).

Both studies included those who were radiologically diagnosed with OA of the knee and who were symptomatic for pain. All had discontinued any other therapeutic treatment; however, both studies allowed participants to continue with paracetamol as required. Interestingly, Baer et al[11] excluded those who were taking glucosamine and/or chondritine; however, Simon et al[19] did not exclude these candidates. One would concur this difference would not affect the overall outcome, showing a change in clinical practice of the actual effect of these additional supplements, with recent clinical guidelines[13] advising against prescribing due to a lack of supporting evidence of their effectiveness. Thus, on-going use by participants would not affect results. In addition to avoid the risk of a placebo effect from rubbing the affected area, both studies advised "40 drops" were put directly onto the painful knee without massage.

Although study by Tiso et al[12] was conducted with much smaller number of participants (20 with 19 completing), it specifically compared oral versus topical ibuprofen, whereas the other 2 trials compared diclofenac. There are limitations to this study, such as it was unblinded and over a very short period of time (2 weeks); yet it does meet the criteria of medium quality as it had a random allocation of participants as a retrospective study. Although not deemed a limitation by the authors, a small unblinded pilot study does not acknowledge the placebo effect or participant preference to the overall results, and it does still support the beneficial qualities of topical NSAIDs; however, in comparison to the other studies, with the lack of acknowledgement of these limitations, it is advisable not to rely heavily on their results to support the hypothesis on the benefits of a topical application. Overall, on the basis of literature reviewed, these 3 studies support the use of a topical application of NSAID, with at least one supporting the use of topical ibuprofen specifically on key areas of the WOMAC scoring (that of pain, stiffness, and function). This minimal number of studies that met a high level of quality supports the need for greater studies on the effect of topical NSAIDs (and for the UK topical ibuprofen as previously discussed) over a longer term (plus 12 weeks).

Inclusion of the cohort study[3] clearly demonstrated, over a wide geographical region, the risks associated with the use of oral NSAIDs. Although this cohort retrospective study is a good example of large data collection resulting in pertinent national data, there are key limitations to the overall outcome. This includes a lack of knowledge of relevant comorbidities (high blood pressure, medical history, body mass index [BMI]) as well as a time scale of use of NSAIDs with respect to incident of myocardial infarction (MI). Had this study been a prospective study, the authors could have afforded a better screening process for the inclusion of patients, which in turn would have contributed to a more robust paper. As a result, this article has been graded as low to medium and would not necessarily meet the robust qualities required of a Cochrane or national guideline; however, for this review, it was important that the discussion about the associated risks of oral NSAIDs be highlighted, and with the size of the study (83 677 participants), and time frame (1999-2006), it afforded a collection of good quality data unbiased by placebo or participant perception.

Although not an ideal primary source of research, 3 reviews,[4,5,14,15] plus 2 Guidance Documents,[1,2] were included. Both Argoff and Gloth[4] and Derry et al[5] concluded that topical preparations are suitable first-line treatments for OA of the knee, although both concluded a lack of long-term studies available in literature (a similar conclusion to our own).

For our discussion on inflammation, OA, and the process of NSAIDs and their affect, Bushra and Aslam[14] and McPhearson and Cimino[15] clearly demonstrated a high level of available resources with a pharmacological and pharmokinetic bias. Studies chosen for these reviews included those with male and female participants within a specific age group (40-85 years). Although the selected data were again limited to short-term parameters of studies up to 12 weeks, all clearly conclude that the evidence (albeit small compared to oral preparation studies) for topical NSAID be of a high level of evidence, further mirrored by multiple International Commissioning papers on the same subject.

Critical evaluation of the proposition work

As discussed, with the risks associated with the overprescription of NSAIDs, and in particular ibuprofen in the patients who aged above 65 years, health care providers have called for an increased restrictions in the sale of oral preparations of this drug. From a Prudent Health care perspective, the inappropriate overprescription of oral ibuprofen for the treatment of knee OA. Topical NSAID's, and for this (UK-based) review, topical ibuprofen, is becoming more widely used as an alternative treatment for OA, and in particular OA of the knee and hand; 7 out of 9 existing guidelines for knee OA recommend this preparation of NSAIDs.[1,2] Subsequently, it has been recommended that the use of topical rather than oral anti-inflammatory drugs be prescribed to those over the age of 65 years due to the associated risks of the oral preparation.

Our aim was to establish that the use of topical ibuprofen is best practice and should therefore be adopted nationally for the management of knee OA. With the aim of a standardized treatment, a selection to ensure a consistent and robust pathway, future involves proofing the management of these patients, by supporting clinicians in their choice of medication.

A need for an updated MRHA pharmacology review is in due part to more recent conflicting research on the safety of over-the-counter analgesics, with studies similar to Franceschi et al[23] that reported oral NSAIDs as responsible for 23.5% of all hospitalizations in this age group (<65 years). As the percentage

of the population above the age of 65 years increases, the long-term nonsurgical management of OA needs addressing. The lifetime of a knee replacement can vary from 15 to 25 years dependent on the level of activity it endures,[24] coupled with the subsequent increase in adverse drug events in community-dwelling patients due to the concurrent age-related conditions,[25] and highlights the need for long-term management.

Conclusions

The best outcome in the treatment of OA is the co-dependence combination of nonpharmacological and pharmacological interventions for the improvement of range, strength, and mobility. There are obvious risks associated with the long-term oral NSAIDs use, although the JFC[13] does mention a small systemic risk in the use of topical ibuprofen, as yet this is only hypothetical rather than evident. There has also been discussion on the efficacy of a topical application due to its issues with penetration through the skin as a barrier. However, these studies are more than 15 years old, and the more recent ones chosen for this literature review, and including the MRHA scientific discussions, reason that the efficacy of the drug in the plasma concentrate at the site of application is significant enough to be recommended in 7 out of 9 International Clinical Guidelines.[7]

It is essential when leading change to engage with everyone who contributes to be aware of any issues faced and support them in solving these problems early on in the process. It is vital to ensure that engagement with all other clinicians be open and positive to ensure all are aware of the need for evidence to support our treatment decisions. Although there are often obstacles and barriers to implementing change, understanding the thought processes behind this is important. Caution is always advised when prescribing, and medication should always be given at the lowest dose for the shortest possible time. As the efficacy of topical Ibuprofen at a local level is not significantly different to oral ibuprofen, the reduced risk of systemic reaction, overdose, and drug interactions make it a suitable first choice for the treatment of this condition. Although we await the more recent review by the MRHA, as clinicians we can carefully reason the research to determine the validity of topical NSAIDs and in particular topical Ibuprofen for the first-line treatment of mild to moderate OA in the United Kingdom.

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REFERENCES

1. National Institute for Health and Clinical Excellence. *Osteoarthritis: The Care and Management of Osteoarthritis in Adults* (NICE Clinical Guideline 59). London, England: National Institute for Health and Clinical Excellence; 2008. http://www.nice.org.uk/nicemedia/pdf/CG59NICEguideline.pdf. Accessed January 5, 2017.
2. Bruyere O, Cooper C, Pelletier J-P, et al. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Semin Arthritis Rheum*. 2014;44:253-363.
3. Olsen AM, Fosbøl EL, Lindhardsen J, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. *Circulation*. 2011;123(20):2226-2235. http://circ.ahajournals.org/content/123/20/2226.full.pdf. Accessed April 12, 2017.
4. Argoff CE, Gloth FM. Topical nonsteroidal anti-inflammatory drugs for management of osteoarthritis in long-term care patients. *Ther Clin Risk Manag*. 2011;7:393-399.
5. Derry S, Moore RA, Gaskell H, McIntyre M, Wiffen PJ. Topical NSAIDs for acute musculoskeletal pain in adults. *Cochrane Database Syst Rev*. 2015;6:CD007402.
6. American Academy of Orthopaedic Surgeons. Treatment of osteoarthritis of the knee (non-arthroplasty): full guideline. *J Am Acad Orthop Surg*. 2013;21:571-576.
7. American Geriatrics Society Panel (AGS) on the Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*. 2009;57:1331-1346.
8. Hochberg MC, Altman RD, April Benkhalti KTM, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012;64:465-474. http://www.rheumatology.org/practice/clinical/guidelines/PDFs/ACR_OA_Guidelines_FINAL.pdf. Accessed March 23, 2017.
9. Jordan KM, Arden NK, Doherty M, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the standing committee for International Clinical Studies Including Therapeutic Trials (ESCISIT) [extended report]. *Ann Rheum Dis*. 2003;62:1145-1155. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1754382/pdf/v062p01145.pdf. Accessed January 5, 17.
10. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage*. 2008;16:137-162. https://www.oarsi.org/sites/default/files/library/2013/pdf/part_ii_oarsi_recommendations_for_management_of_hipknee_oa_2007.pdf. Accessed December 10, 2016.
11. Baer PA, Thomas LM, Shainhouse Z. Treatment of osteoarthritis of the knee with a topical diclofenac solution: a randomised controlled, 6-week trial. *BMC Musculoskelet Disord*. 2005;6:44.
12. Tiso RL, Tong-Ngork S, Fredlund KL. Oral versus topical Ibuprofen for chronic knee pain: a prospective randomized pilot study. *Pain Physician*. 2010;13:457-467.
13. Joint Formulary Committee. *British National Formulary*. 68th, 69th, 70th ed. London, England: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2014, 2015, 2016.
14. Bushra R, Aslam N. An overview of clinical pharmacology of ibuprofen. *Oman Med J*. 2010;25:155-1661. www.ncbi.nlm.nih.gov. Accessed February 19, 2017.
15. McPherson ML, Cimino NM. Topical NSAID formulations. *Pain Med*. 2013;14:S35-S39.
16. *Voltaren Gel* [package insert]. Chadds Ford, PA: Endo Pharmaceuticals Inc; 2009. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022122s006lbl.pdf. Accessed March 10, 2016.
17. Amdipharm Mercury Company Limited. SPC oral ibuprofen 400mg. https://www.medicines.org.uk/emc/search/?q=ibuprofena=178. Updated 2014. Accessed February 23, 2016.
18. Amdipharm Mercury Company Limited. SPC topical ibuprofen 10%. https://www.medicines.org.uk/emc/search. Updated 2014. Accessed February 23, 2016.
19. Simon LS, Grierson LM, Naseer Z, Bookman AAM, Zev Shainhouse J. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (DMSO) compared with those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis. *Pain*. 2009;143:238-245.
20. MHRA scientific discussion: Ibuleve Pain relief gel 5%. PL 00173/0408 application for marketing and sale. MHRA-UKPAR; July 6, 2010.
21. MHRA scientific discussion: Nurofen Maximum Pain relief gel 10%. PL 10972/0089 application for marketing and sale. *MHRA-UKPAR;* July 27, 2012.
22. Jadad AR, Carroll D, Moore A, McQuay H. Developing a database of published reports of randomised clinical trials in pain research. *Pain*. 1996;66:239-246.
23. Franceschi M, Scarelli C, Niro V, et al. Prevalence, clinical features and avoidability of adverse drug reactions as a cause for admission to a geriatric unit: a prospective study of 1756 patients. *Drug Saf*. 2008;31:545-556.
24. Sabouret P, Lavoie F, Cloutier JM. Total knee replacement with retention of both cruciate ligaments: a 22-year follow-up study. *Bone Joint J*. 2013;95:917-922. doi:10.1302/0301-620X.95B7.30904.
25. Bayoumi I, Howard M, Holbrook AM, Schabort I. Interventions to improve medication reconciliation in primary care. *Ann Pharmacother*. 2009;43:1667-1675.