Volume 21, Issue 2

Topical Anti-Inflammatories: Analgesic Options for Arthritis Beyond NSAIDs

Diclofenac gel and phytochemicals provide holistic alternatives to managing inflammatory pain in patients unable to tolerate or obtain relief with traditional medications.

CITE THIS ARTICLE
Thorfinnson H, Dalton S, Atkinson T. Topical Anti-Inflammatories: Analgesic Options for Arthritis Beyond NSAIDs. Pract Pain Manag. 2021;21(2).

Oct 20, 2021
Hannah Thorfinnson, PharmD
Shawn Dalton, PharmD
Timothy J. Atkinson, PharmD, BCPS, CPE
Clinical Pharmacy Specialist, Pain Management
Topicals are growing in preference given their localized drug delivery and low systemic absorption. Both aspects result in a more favorable side effect profile for patients seeking pain relief.

Topical medications differ from transdermal medications in that transdermal drug delivery systems are designed to deliver drugs systemically through cutaneous absorption from external application. Topical preparations are designed for localized effects, therefore minimizing systemic effects.

Topicals are available in a wide variety of formulations including:

- gels
- foams
- creams
- ointments
- patches, and more.

Pain medications, particularly those used for a long duration of time to manage chronic pain conditions, can have serious and potentially life-threatening adverse effects. As patients age and their lists of comorbid disease states grow, medication management becomes increasingly more complex and options for pharmacological interventions diminish. For this reason, a topically applied and localized drug effect may be favorable.

Topical Analgesics: Trends and Limitations of Use

A recent trend in guidelines favors topical formulations when evidence for efficacy exists. One example is the American College of Rheumatology (ACR) guidelines for hand and knee osteoarthritis which recommend the use of topical NSAIDs ahead of oral NSAIDs due to an improved side effect profile and comparable efficacy, especially in elderly populations.[1,2]

Over-the-counter topical analgesics offer patients an easily accessible alternative for treating painful conditions, including osteoarthritis, musculoskeletal pain, and neuropathic pain, although OTC products typically have fewer studies establishing their safety and efficacy. The literature does include reviews of topical pain preparations, however, given that the bulk of the data available surrounds prescription-strength formulations, these reviews have focused mainly in that area.[3,4]

Additionally, many review articles exclude small studies as they have low power to estimate treatment effect with accuracy; that said, achieving a >50% reduction in pain in a trial is often considered an unrealistic expectation in pain management.[5]

Together, these limitations have reduced the data available outside of commonly used topicals such as lidocaine, capsaicin, and NSAIDs, with which most pain specialists are already very familiar. (Editor's Update: FDA issued a recall of super potent lidocaine HCl topical solution 4%, 50 mL on Oct 20, 2021). While practitioners have several options for topical treatment of neuropathic and muscular pain, they are confined to the use of topical NSAIDs for inflammatory conditions. Options are further constricted when patients prefer to avoid NSAIDs, even topical ones, because of the plethora of online information warning them of the harms associated with use.

This article aims to address the safety concerns around topical NSAIDs and provide a review of alternative topical anti-inflammatories available for patients preferring a more holistic option.

Topical NSAID Options Reduce Safety Concerns

Diclofenac Gel 1% for Osteoarthritis and Rheumatoid Arthritis

Many painful conditions, including osteoarthritis (OA) and rheumatoid arthritis (RA) are inflammatory in nature, with the inflammation localized to specific areas of the body. NSAIDs work by inhibiting cyclooxygenase enzymes involved in the synthesis of inflammatory mediators known as prostaglandins. These drugs are widely used in the treatment of pain with a variety of indications but are often limited by their adverse effect (AE) profile, including gastrointestinal disturbance, cardiotoxicity, and renal toxicity.[6–8]

Topical NSAIDs with low systemic absorption, however, offer anti-inflammatory effects locally (at the site of inflammation) while minimizing systemic adverse effects. Diclofenac gel is the only topical NSAID available in the United States and, until February 2020, was only available with a prescription. FDA approved diclofenac 1% for OTC use through the Rx-to-OTC switch process.[9]The approval was largely based on studies that examined the safety of this medication and concluded that it is safe for laypersons to use without a prescription.

A pharmacokinetic study comparing diclofenac 1% gel to oral diclofenac found significantly less systemic absorption with topical diclofenac.[10] When compared to a 150 mg daily dose of oral diclofenac, the Area Under the Curve (AUC) of a 48 g daily dose and 28 g daily dose of 1% diclofenac gel was 5- and 17-fold less, respectively. (AUC is a pharmacokinetic measurement of drug concentration in the body over time and often associated with adverse effect profiles of drugs.) Adverse effects in this study were limited to local reactions including dermatitis, erythema, pruritis, and paresthesia.

Diclofenac 1% gel has been extensively studied as it was previously a prescription product, and the 1% gel has been shown to decrease pain intensity in hand and knee OA.[11,12] Topical diclofenac has even been recommended ahead of oral NSAIDs in recent OA guidelines for knee arthritis due to the favorable side effect profile of topical diclofenac with comparable efficacy.[1,2] Given the multitude of review articles denoting the benefit of topical NSAIDs, this review will not delve further into the data surrounding efficacy.

Practical Takeaway: Given the well-established efficacy of topical diclofenac gel and minimal adverse effect profile, consider as a first-line agent for inflammatory pain in small joints such as knees and hands and a reasonable second-line agent for patients refractory to or unable to tolerate oral NSAIDs.

Topical Phytochemicals: *Arnica montana*, Comfrey, Sesame

Although the literature available for the safety of diclofenac topical gel suggests a low risk of systemic AEs, some patients may prefer more holistic options, which are collectively referred to as phytochemicals. The term phytochemical broadly refers to naturally occurring compounds in plants (from Greek *phyto,* meaning "plants"). These compounds play a biological role in helping the plant survive in nature by thwarting off harm.[13]

Phytochemicals have been used for centuries in traditional medicine, both topically and orally, for various conditions. They are believed to have anti-inflammatory and analgesic properties but there is a lack of data to support use or even provide a potential mechanism for which they elicit these properties. A few phytochemicals, however, have been studied more extensively than even commonly recommended OTC topicals, including lidocaine and capsaicin, and are therefore worthy of consideration:

- *Arnica montana*
- Symphytum (comfrey)
- *Sesamum indicum* (sesame).

Arnica has been studied for the treatment of knee osteoarthritis.

Arnica montana and Arthritis

_Arnica montana_is a flowering plant in the sunflower family, and is sometimes called wolf's bane, leopard's bane, mountain tobacco, and mountain arnica.[13] Its active ingredients are the sesquiterpene lactones, which have been shown to exhibit anti-inflammatory properties by inhibiting the activation of nuclear factor (NF)-kappaB, a transcription factor intimately involved in inflammation.[14] Arnica is found in many OTC gels and creams, alone and in combination with other active ingredients. It appears to be the most commonly utilized phytochemical for pain relief and has positive data to support its use in arthritis pain.[13]

Arnica has been studied for the treatment of knee osteoarthritis in an open, multicenter trial conducted by Knuesel and colleagues.[15] This trial demonstrated statistically significant reductions in pain, stiffness, and function subscales from the overall Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. Although results were significant, without a control group, it is difficult to discern efficacy as placebo effect can be strong in areas of pain management. With that said, the AEs reported that were deemed to be related to the study drug were all local reactions including itching, rash, pruritis, and dry skin – all of which were mild in severity.

Arnica has also been studied in a head-to-head comparison with topical NSAIDs which are first-line options in managing arthritis pain. Widrig and colleagues conducted a double-blind, RCT comparing ibuprofen 5% gel to *Arnica montana* fresh herbal tincture 50 g/100 g gel in patients with osteoarthritis of the hand.[16] Patients applied the gel to painful areas of the hands three times daily for three weeks and were evaluated for pain intensity using a visual analog scale as well as general hand functionality. For both endpoints, arnica gel was found to be non-inferior to topical ibuprofen.

Practical Takeaway: Given the favorable side effect profile and demonstrated efficacy, utilization of Arnica gel may be considered in patients with arthritic pain who are unable to tolerate topical NSAIDs or as an alternative for those who do not benefit from topical NSAIDs.

Symphytum (Comfrey) as an Adjunct Therapy for Osteoarthritis

Comfrey is a perennial flowering plant of the Borage family that has been used in traditional medicine both topically and orally for arthritic pain, broken bones, contusions, distortions, and strained muscles.[13] Comfrey has been referred to as knitbone or boneset, and the name symphytum is derived from the Greek word *symphis,* meaning the process of growing together. Today, comfrey is only available for topical use and can be found over the counter in various creams, ointments, oils, liniments, and salves.

In 2001, the FTC issued a warning for products containing comfrey, recommending that products for internal use be removed from the market.[17] There had been several case reports of hepatic veno-occlusive disease leading to cirrhosis and eventually liver failure. Comfrey contains pyrrolizidine alkaloids, which are toxic compounds that are potentially hepatotoxic. Because of this, FDA mandated that products containing comfrey come affixed with the following:

"WARNING: External Use Only. Consuming this product can cause serious liver damage. This product contains comfrey. Comfrey contains pyrrolizidine alkaloids, which may cause serious illness or death. This product should not be taken orally, used as a suppository, or applied to broken skin."

It should be noted that comfrey plants devoid of pyrrolizidine alkaloids have been produced in cultivation by selective breeding and many of the products available today do not contain pyrrolizidine alkaloids.[18]

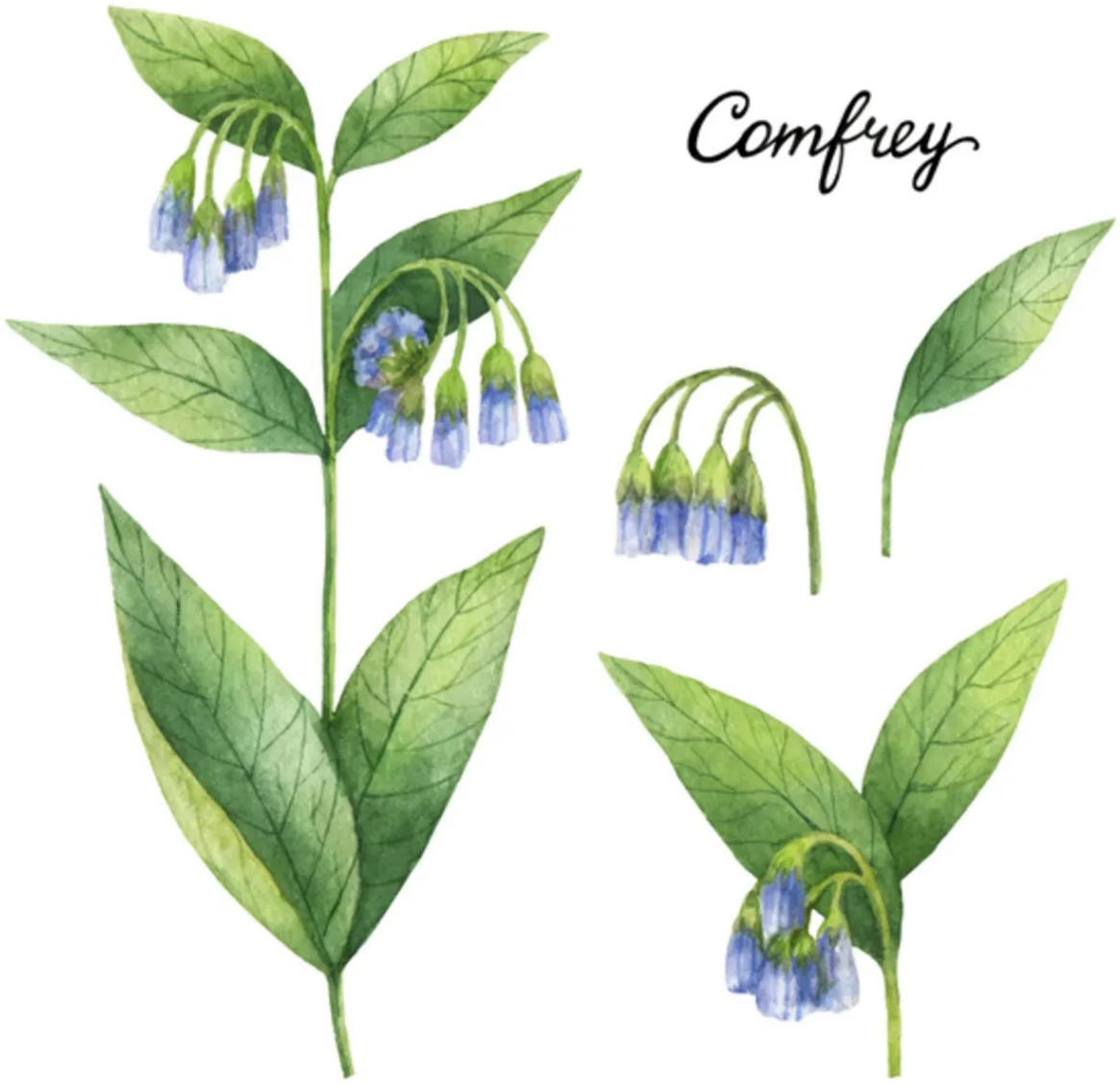
The mechanism by which comfrey-containing products exert their analgesic effects is thought to be reliant on the active ingredient, rosmarinic acid. Rosmarinic acid has been studied in vitro

with results that suggest this compound's ability to inhibit the expression of cytokines may yield anti-inflammatory properties.[19] Rosmarinic acid has also been shown to inhibit prostaglandin synthesis in vivo, which further explains the anti-inflammatory properties denoted with comfrey containing products.[20]

Comfrey-containing topical agents may be effective for pain reduction in OA of the knee as well as acute pain associated with injury. A large, randomized, double-blind and placebo-controlled clinical trial conducted by Grube et al compared three times daily topical administration of an ointment containing comfrey to placebo in patients with knee OA.[21] Researchers found that the comfrey-containing ointment significantly reduced scores on a visual analogue scale (VAS) by 51.6 mm, which was greater than a 50% reduction from baseline compared to placebo with a 10.1 mm reduction. WOMAC scores for pain, stiffness, physical function, and overall scores significantly improved for patients in the comfrey group as well. This study required that patients discontinue all other analgesic medications and therefore results presented are that of comfrey as a sole analgesic. Adverse events were reported more frequently in the placebo group than in the comfrey group, although liver function was not assessed.

These results were confirmed by Laslett and colleagues in a study of similar design and magnitude.[22] This study, however, demonstrated less reduction in VAS scores between placebo and comfrey groups (9.9 mm between group difference). In a post-hoc analysis, researchers concluded that there was a larger reduction in VAS for patients with early osteoarthritis (grade 0-1), which may attribute to the difference between studies as the trial conducted by Grube et al had a larger population of patients with early arthritis. Additionally, the authors concluded that the difference may be attributed to their use of comfrey-containing ointment as an adjunct analgesic agent and thus less impactful on VAS scores. Laslett et al did obtain serum chemistry results and reported no significant difference between treatment and placebo.

Practical Takeaway: Given the demonstrated efficacy and minimal adverse effect profile, comfrey may be considered a reasonable recommendation in patients with osteoarthritis as an adjunct therapy or in those patients unable to tolerate first-line medications. Although AEs in the two studies shared above are low, given the toxic effects of pyrrolizidine alkaloids and the minimal testing conducted on OTC products, it is advisable to routinely monitor hepatic functioning and utilize caution in patients with elevated baseline risk.



Comfrey may reduce knee pain and inflammation related to osteoarthritis.

Comfrey for Acute Pain Care

Comfrey-containing products have also been studied with success in acute pain settings. In 2004, Kucera, et al, conducted a randomized, multicenter, double-blind and reference-controlled study analyzing the effects of a 10% comfrey root extract cream compared to a low-dose 1% comfrey containing reference cream.[23] They assessed reduction of pain associated with a sprained ankle utilizing a VAS-10. Statistical and clinical significance were achieved for the reduction of VAS scores for pain when moving, pain at rest, and functional restrictions.

In 2005, Kucera, et al, used the same concentrations of cream to study pain reduction in acute myalgia located in either the upper or lower regions of the back.[24] Pain in motion, pain on

palpation, pain at rest, and functional impairment were evaluated at day 0, days 4-5, and days 8-10. For all endpoints, the 10% comfrey root extract cream was significantly more pronounced than with the reference product and was considered to be highly clinically relevant by investigators. Most patients reported the onset of pain relief to be quick to very quick, which is an interesting finding for a topical preparation targeting the inflammatory cascade.

Gianetti and colleagues conducted a similar study utilizing placebo control as opposed to a reference product in a double-blind, multicenter, RCT.[25] Investigators assessed pain in motion for acute upper and lower back injuries, similar to Kucera et al's work. The primary endpoint in this trial was also pain in motion as assessed by VAS with secondary outcomes including pain at rest and global assessment of efficacy by the patient and investigator. Results for the primary outcome of this study were highly significant with an average reduction in VAS score of approximately 95.2% in the comfrey-containing arm compared to a 37.8% reduction in the placebo arm. Results also demonstrated a rapid onset of action with a 33% reduction experienced within the first hour of application in the comfrey-containing group. Adverse events reported in this study were mild in nature and were not significantly different than that of placebo.

Additionally, topical comfrey-containing cream has been compared to diclofenac gel for acute pain associated with sprained ankle by Predel et al, and demonstrated non-inferiority for reduction in VAS at rest with a 92.01% reduction in VAS in the comfrey-containing group compared to an 84.96% reduction in the diclofenac group after 7 days of treatment.[26] This was a multicenter, RCT of 164 patients with average age less than 30 years presenting within 6 hours of an acute, uncomplicated unilateral ankle sprain. Non-inferiority was also demonstrated in reduction in VAS in motion from baseline with an 83.2% reduction in the comfrey arm compared to 73.27% in diclofenac arm. Adverse effects of the comfrey-containing cream were most notable for a mild reddening of the skin after application.

Practical Takeaway: Based on the results of this study along with those presented by Kucera et al, and Gianetti et al, utilization of comfrey-containing products for acute inflammatory pain may be considered in patients who are unable to utilize FDA-approved medications for this indication. Given that OTC diclofenac gel tends to be more cost effective than comfrey-containing cream, patients may prefer diclofenac gel if not contraindicated.

Sesame may help to reduce knee pain. (iStock)

Sesamum indicum (Sesame) for Osteoarthritis; Comparison to Diclofenac Gel

Sesame is a flowering plant cultivated for its seeds, which are processed to extract oil. Sesame oil has been used in traditional medicine to relieve pain from inflammatory conditions.[13] Sesame seeds contain lignans such as sesamin, sesamol, sesaminol and sesamolin – all of which have been extensively studied and are thought to possess anti-inflammatory properties along with several other mechanisms in chronic disease.

These lignans have several proposed mechanisms for their anti-inflammatory properties including inhibition of inflammatory cytokines (namely IL-6, IL-1β and TNF-α).[27] These inflammatory cytokines stimulate matrix metalloproteinases (MMPs), which play a major pathological role in the cartilage destruction characteristic of osteoarthritis. Sesamol has been shown to have chondroprotective properties both in vitro and in animal studies by attenuating the expression of MMPs by inhibiting these important inflammatory cytokines.[28,29]

Most of the studies conducted on the clinical impact of sesame oil have been with oral ingestion but two studies published with promising data support its topical use. An RCT conducted by Bigdeli Shamloo et al in patients with pain associated with blunt force trauma demonstrated a significant difference in pain scores utilizing a VAS.[30] The group receiving treatment with 100% pure sesame oil also utilized less NSAIDs in the management of their acute pain compared to control group. Statistical significance demonstrated by this study may have been heavily influenced by the placebo effect as it was not placebo controlled and was therefore unblinded.

Askari and colleagues conducted a randomized, placebo-controlled, non-inferiority clinical trial to compare topically applied sesame oil to diclofenac gel in patients with knee OA.[31] Outcomes measured were knee pain utilizing a VAS, WOMAC scores, knee joint's flexion angle, 8 meter walk test, and a number of additional analgesics required for pain control. Sesame oil was non-

inferior to topical diclofenac regarding WOMAC pain scores, knee joint's flexion angle, and 8 meter walk test but did not meet non-inferiority criteria for VAS or WOMAC stiffness.

Practical Takeaway: The results of this study along with the results presented by Bigdeli Shamloo et al by no means indicate that sesame oil be used in place of diclofenac gel as a first-line agent in the management of osteoarthritis, but neither trial reported any significant side effects associated with use and thus it may be used in addition to or in patients who have failed topical diclofenac. Diclofenac gel can also be cost prohibitive to many patients and sesame oil may provide a more feasible approach to management of their osteoarthritis symptoms.

Conclusion

Managing pain related to inflammatory conditions can pose quite a challenge as NSAID therapy is often the cornerstone for treatment. Oral NSAIDs are limited by their broad array of adverse effects, especially at higher doses for extended periods of time, which has led to the recent ACR guidelines for knee osteoarthritis favoring topical NSAIDs ahead of oral NSAIDs.

Given that the only FDA approved topical NSAID available in the United States is diclofenac 1% gel, providers often feel limited in available options for inflammatory conditions such as osteoarthritis and rheumatoid arthritis. Diclofenac 1% gel has the most robust data to support the safety and efficacy for its use and it should be considered first-line despite the non-inferiority trials that have suggested similar efficacy with multiple phytochemicals.

While the phytochemicals such as *Arnica montana*, *symphytum (comfrey)* and *Sesamum indicum (sesame)* do not appear in analgesic management guidelines at this time, they do offer alternative options for patients who fail topical diclofenac, are unable to tolerate NSAIDs, or who prefer a more holistic option.

This article was originally published February 22, 2021 and most recently updated October 20, 2021.

1. National Institute for Health and Care Excellence. Osteoarthritis: Care and management in adults. NICE clinical guideline 177 (guidance.nice.org.uk/cg177). London: Royal College of Physicians, 2014.
2.
3. Hochberg MC, Altman RD, April KT, 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(4):465-474. doi:10.1002/acr.21596
4.

5. Jorge LL, Feres CC, Teles VE. Topical preparations for pain relief: efficacy and patient adherence. _J Pain Res_. 2010;4:11–24. Published 2010 Dec 20. doi:10.2147/JPR.S9492
6.
7. Wang K, LaBeff L, Thomas AM, and Mena Raouf M. Topical Analgesics for Chronic Pain Conditions. _Practical Pain Manage_. 2018;18(5).
8.
9. Derry S, Wiffen PJ, Kalso EA, et al. Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews. _Cochrane Database Syst Rev_. 2017;5(5):CD008609. Published 2017 May 12. doi:10.1002/14651858.CD008609.pub2
10.
11. Farkouh ME, Greenberg BP. An evidence-based review of the cardiovascular risks of non-steroidal anti-inflammatory drugs. _Am J Cardiol_ 2009;103:1227–1237.
12.
13. Harirforoosh S, Jamali F. Renal adverse effects of nonsteroidal anti-inflammatory drugs. _Expert Opin Drug Saf_. 2009;8(6):669-681. doi:10.1517/14740330903311023
14.
15. García Rodríguez LA, Barreales Tolosa L. Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. _Gastroenterology_. 2007;132:498–506.
16.
17. Turney, Amanda. FDA Approves Three Drugs for Nonprescription Use Through Rx-to-OTC Switch Process. _U.S. Food and Drug Administration_, FDA, 14 Feb. 2020, www.fda.gov/news-events/press-announcements/fda-approves-three-drugs-nonprescription-use-through-rx-otc-switch-process.
18.
19. Kienzler JL, Gold M, Nollevaux F. Systemic bioavailability of topical diclofenac sodium gel 1% versus oral diclofenac sodium in healthy volunteers. *J Clin Pharmacol*. 2010 Jan;50(1):50-61. doi: 10.1177/0091270009336234. Epub 2009 Oct 19. PMID: 19841157.

20. Altman RD, Dreiser RL, Fisher CL, et al. Diclofenac sodium gel in patients with primary hand osteoarthritis: a randomized, double-blind, placebo-controlled trial. *J Rheumatol*. 2009;36(9):1991-9. [DOI: 10.3899/jrheum.081316]

21. Baraf HS, Gloth FM, Barthel HR, et al. Safety and efficacy of topical diclofenac sodium gel for knee osteoarthritis in elderly and younger patients: pooled data from three randomized, double-blind, parallel-group, placebo-controlled, multicentre trials. _Drugs Aging._2011;28(1):27-40.

22. Cameron M, Chrubasik S. Topical herbal therapies for treating osteoarthritis. Cochrane Database Syst Rev. 2013;(5):CD010538. doi: 10.1002/14651858.CD010538.

23. Lyss G, Knorre A, Schmidt T J, Pahl H L, Merfort I. The anti-inflammatory sesquiterpene lactone helenalin inhibits the transcription factor NF-kappaB by directly targeting p65. *J Biol Chem*. 1998: 273: 33508–33516.

24. Knuesel O, Weber M, Suter A. Arnica montana gel in osteoarthritis of the knee: an open, multicenter clinical trial. *Adv Ther*. 2002 Sep-Oct;19(5):209-18. doi: 10.1007/bf02850361

25. Widrig, R., Suter, A., Saller, R. et al. Choosing between NSAID and arnica for topical treatment of hand osteoarthritis in a randomized, double-blind study. *Rheumatol Int*. 2007;27:585. doi: 10.1007/s00296-007-0304-y

26. US Federal Trade Commission. Release: FTC Announces a Second Case Focusing on Safety Risks of Comfrey Products Promoted via Internet. 13 July 2001. Available at: https://www.ftc.gov/news-events/press-releases/2001/07/ftc-announces-second-case-focusing-safety-risks-comfrey-products

27. Staiger C. Comfrey: a clinical overview. *Phytother Res*. 2012;26(10):1441-1448. doi:10.1002/ptr.4612

28. Lee J, Jung E, Kim Y, et al. Rosmarinic acid as a downstream inhibitor of IKK-beta in TNF-alpha-induced upregulation of CCL11 and CCR3. *Br J Pharmacol*. 2006;148(3):366-375. doi:10.1038/sj.bjp.0706728

29. Englberger W, Hadding U, Etschenberg E, et al. Rosmarinic acid: a new inhibitor of complement C3-convertase with anti-inflammatory activity. *Int J Immunopharmacol*. 1988;10:729–737.

30. Grube B, Grünwald J, Krug L, Staiger C. Efficacy of a comfrey root (Symphyti offic. radix) extract ointment in the treatment of patients with painful osteoarthritis of the knee: results of a double-blind, randomised, bicenter, placebo-controlled trial. *Phytomedicine*. 2007 Jan;14(1):2-10. doi: 10.1016/j.phymed.2006.11.006.

31. Laslett LL, Quinn SJ, Darian-Smith E, et al. Treatment with 4Jointz reduces knee pain over 12 weeks of treatment in patients with clinical knee osteoarthritis: A randomised controlled trial. *Osteoarthr Cartil*. 2012;20:1209–1216. doi: 10.1016/j.joca.2012.07.019

32. Kucera M, Barna M, Horacek O, et al. Efficacy and safety of topically applied Symphytum herb extract cream in the treatment of ankle distortion: Results of a

randomised controlled clinical double blind study. *Wien Med Wochenschr.* 2004;154: 498–507.

33. Kucera M, Barna M, Horácek O, et al. Topical symphytum herb concentrate cream against myalgia. A randomized controlled double blind clinical study. *Adv Ther.* 2005;22:681–692.

34. Giannetti BM, Staiger C, Bulitta M, Predel HG. Efficacy and safety of a comfrey root extract ointment in the treatment of acute upper or lower back pain: results of a double-blind, randomised, placebo controlled, multicentre trial. *Br J Sport Med*. 2010;44:637–641.

35. Predel HG, Giannetti B, Koll R, et al. Efficacy of a comfrey root extract ointment in comparison to a diclofenac gel in treatment of ankle distortions: results of an observer-blind, randomized, multicenter study. *Phytomedicine*. 2005;12:707–714.

36. Wu MS, Aquino LBB, Barbaza MYU, et al. Anti-Inflammatory and Anticancer Properties of Bioactive Compounds from *Sesamum indicum* L.-A Review. *Molecules*. 2019;24(24):4426. doi:10.3390/molecules24244426

37. Lu YC, Jayakumar T, Duann YF, et al. Chondroprotective role of sesamol by inhibiting MMPs expression via retaining NF-ϰB signaling in activated SW1353 cells. J Agric Food Chem. 2011 May 11;59(9):4969-78. doi: 10.1021/jf1046738.

38. Phitak T, Pothacharoen P, Settakorn J, et al. Chondroprotective and anti-inflammatory effects of sesamin. Phytochemistry. 2012 Aug;80:77-88. doi: 10.1016/j.phytochem.2012.05.016.

39. Bigdeli Shamloo MB, Nasiri M, Dabirian A, et al. The Effects of Topical Sesame (Sesamum indicum) Oil on Pain Severity and Amount of Received Non-Steroid Anti-Inflammatory Drugs in Patients With Upper or Lower Extremities Trauma. *Anesth Pain Med*. 2015 Jun 22;5(3):e25085. doi: 10.5812/aapm.25085v2. PMID: 26161326; PMCID: PMC4493737.

40. Askari A, Ravansalar SA, Naghizadeh MM, et al. The efficacy of topical sesame oil in patients with knee osteoarthritis: A randomized double-blinded active-controlled non-inferiority clinical trial. *Complement Ther Med*. 2019 Dec;47:102183. doi: 10.1016/j.ctim.2019.08.017.

Related

Chronic Pelvic Pain Aug 25, 2021
Chronic Overlapping Pelvic Pain Disorders: Differential Diagnoses and Treatment

Kathryn A. Witzeman, MD, FACOG

Opioids Mar 2, 2021

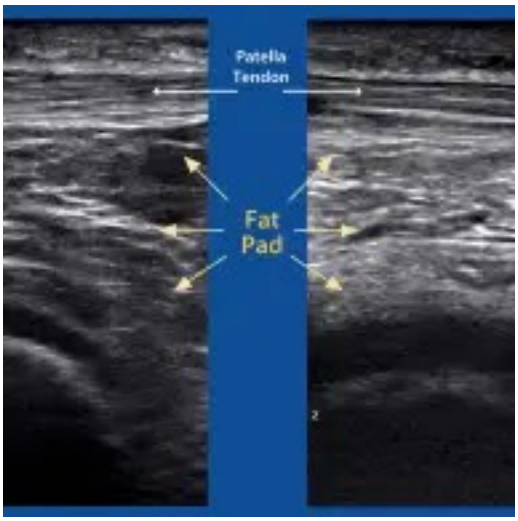
Fentanyl Transdermal Patch: Variability is Key When Prescribing

Angele Ryan, MD

Knee OA Mar 2, 2021

Autologous Adipose-Derived Biocellular (Stem Cell-Rich) Prolotherapy into Hoffa's Fat Pad Improves Knee Osteoarthritis

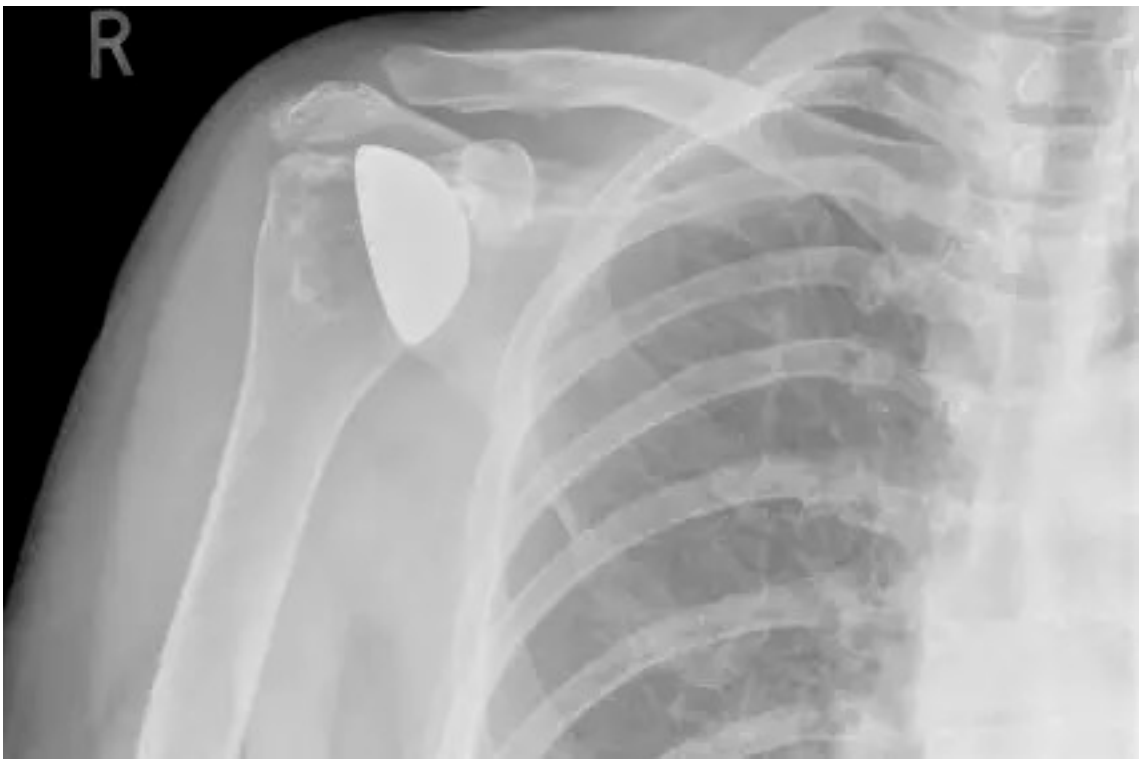
Donna Alderman, DO



Non-OpioidsSep 8, 2021
The Potential of Vocacapsaicin Injections for Knee Pain

Olivia Higgins, PharmD Candidate

Editor's Pick



Research Insights: Advances in Shoulder Arthroplasty and Revision SurgeryMar 2, 2021
Research Insights: Advances in Shoulder Arthroplasty and Revision Surgery

Christine Rhodes, MS

Editor's Pick

Addiction MedicineApr 28, 2021

Advanced Practitioners, MAT and the DATA Waiver Debate

Jeremy A. Adler, DMSc, PA-C, DFAAPA

Editor's Pick

OsteoarthritisMar 2, 2021

Research Insights: How to Address Osteoarthritis Treatment Gaps in Women

PPM Editorial

Editor's Pick

Chronic Pelvic Pain Aug 25, 2021

Chronic Overlapping Pelvic Pain Disorders: Differential Diagnoses and Treatment

Kathryn A. Witzeman, MD, FACOG