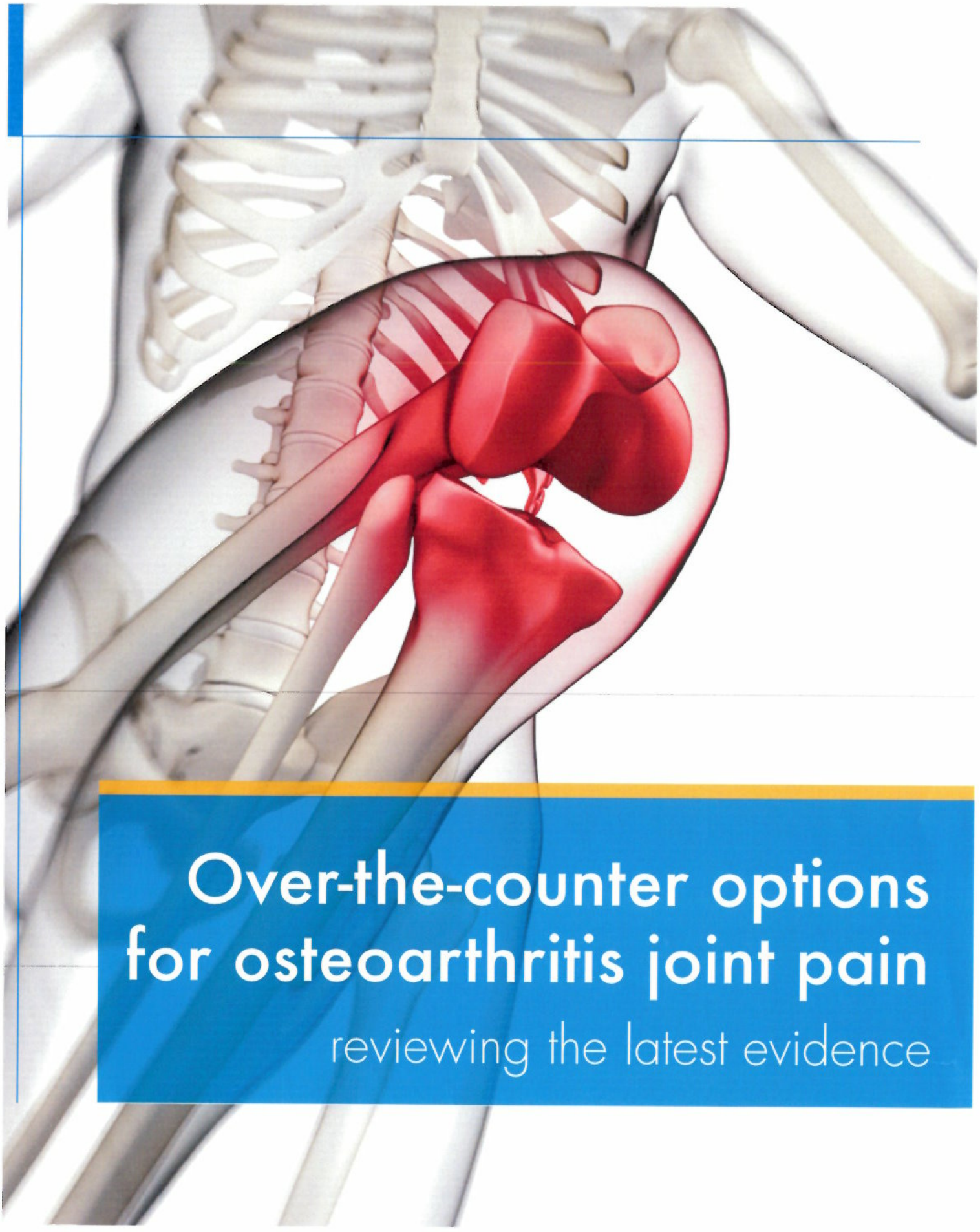

Over-the-counter options for osteoarthritis joint pain

reviewing the latest evidence

Introduction

Dr Rod Hughes, Consultant Rheumatologist, Ashford and St. Peter's Hospitals NHS Foundation Trust

Osteoarthritis (OA) continues to exert a heavy toll on patients and healthcare providers across the UK. A variety of treatment options exist, with non-pharmacological interventions fixed firmly at the core of current guidance[1]. The 2008 National Institute for Health and Care Excellence (NICE) guidelines for the management of adults with OA were due to be updated in 2014, with significant changes proposed – particularly in relation to the use of paracetamol. NICE recommended removing paracetamol as a first-line option for the management of OA, with stark warnings of its toxicity, causing consternation amongst patients and prescribers alike. NICE eventually chose to delay its proposed update on the guideline section relating to the pharmacological management of OA, pending completion of a review by the Medicines and Healthcare Products Regulatory Agency (MHRA) on the safety of over-the-counter (OTC) analgesics. This left many of us unsure what treatment options remained.

In an effort to alleviate the current confusion around OTC options for the management of OA and provide simple recommendations for all healthcare professionals based on the latest evidence, an advisory board of UK pain specialists, rheumatologists and pharmacists was convened. Our aim was to consider how OTC medications and nutritional supplements (nutraceuticals) might be used optimally to support patients in their efforts to self-manage their OA. It was agreed that a review of the latest evidence for OTC options for joint pain in OA would be valuable, helping healthcare professionals offer a more holistic approach to the management of OA. We hope this publication, which was developed with the assistance of three of the original advisory board members and reflects the advisory board discussions, is useful.

Publication contributors

Dr Rod Hughes - Chair

Consultant Rheumatologist at St Peter's Hospital in Chertsey, Surrey

An instrumental member of the Regional Advisory Board in Osteoporosis and a Medical Advisor to the West Surrey National Osteoporosis group, Dr Hughes is active in the research of osteoporosis and the health service's role in rheumatology. Dr Hughes has held the position of Trustee on the executive board and council of the British Society for Rheumatology, he was also the President of the Rheumatology and Rehabilitation section of the Royal Society for Medicine.

"Many OTC products work well for individual patients. Joint supplements and other OTC medications have an important role to play in the management of OA"

Dr Martin Johnson

Clinical Lead for Pain at Royal College of General Practitioners, Honorary Secretary to Council at British Pain Society, Co Chair of the Chronic Pain Policy Coalition.

Dr Johnson was a GP for 29 years (until 2014) and now is Senior Medical Director in a research organisation. He is Honorary Secretary to the British Pain Society and the RCGP Clinical Lead for Pain. Also as the Co-chair of the Chronic Pain Policy Coalition, he is helping to drive national issues surrounding pain management.

"Self-management is really, really important in OA. Patients should be educated about how they can help to improve their own symptoms"

Dr John Dickson

GP Community rheumatologist, Clinical advisor to the NICE guideline development group

Dr Dickson was co-founder of The Primary Care Rheumatology Society (PCR) and has served as president and business manager. He was a Clinical Advisor to NICE for OA Management Guidelines from April 2006 to February 2008. He has co-authored four books on OA and Rheumatology and has been involved in numerous studies and clinical publications. He is also an honorary senior lecturer at Bradford University for the Diploma in Musculoskeletal Medicine which he and four others set up specifically for training GPSIs.

"We need to take a more holistic, multimodal approach to OA care – personalising treatment and combining a variety of interventions to the greatest effect"

The burden of joint pain in OA

Osteoarthritis (OA) is a painful inflammatory joint condition that causes significant disability and markedly reduces quality of life. The condition is characterised by localised loss of cartilage, remodelling of adjacent bone and associated inflammation and there is associated marked muscle wasting. It has been estimated that 8.75 million people in the UK have sought treatment for OA, which represents approximately one-third of the population over the age of 45 years[ii]. Two million adults per year visit their GP because of OA[i].

A variety of different pharmacological and non-pharmacological treatment options exist[i] (Table 1). Healthcare professionals are encouraged to take a holistic approach to the assessment and management of patients with OA, considering the impact of a wide range of clinical, social, and personal factors[i]. Non-pharmacological management options, such as weight loss and physical activity, are considered core interventions, with prescription and non-prescription medications added when required[i].

TABLE 1. Current NICE guidelines for the management of OA (NICE, 2014)

1. Take a holistic approach to the assessment and management of OA
2. Offer patient information and agree self-management strategies
3. Offer advice on core treatments, including access to appropriate information, activity and exercise and interventions to achieve weight loss

Non-pharmacological

✓	Thermotherapy
✓	Exercise (local muscle strengthening & general aerobic fitness)
✓	Manipulation and stretching
✓	Weight loss if obese or overweight
✓	Electrotherapy (TENS)
✓	Aids & devices (footwear, insoles, bracing/joint supports, assistive devices)
✗	Acupuncture
✗	Arthroscopic lavage and debridement (unless a clear history of mechanical knee locking)

Pharmacological*

	1st Choices
✓	Paracetamol
✓	Topical NSAIDs
	2nd Choices
✓	Oral NSAID/COX-2 inhibitors
✓	Topical capsaicin
✓	Opioids
✓	Corticosteroid joint injections

	Not recommended
✗	Rubefacients
✗	Hyaluronan joint injections
✗	Glucosamine or chondroitin

*A full review of the evidence on the pharmacological management of OA will be conducted by NICE after the MHRA (Medicines and Healthcare Products Regulatory Agency) completes its review of the safety of OTC analgesics.

Over-the-counter medications, nutritional supplements and other complementary medicines are increasingly popular amongst sufferers of OA and a wide range of options are available[iii]. According to Arthritis Research UK, approximately 60% of people with arthritis and musculoskeletal conditions have tried complementary and alternative medications possibly reflecting the long-term nature of the condition and dissatisfaction with prescribed treatments. Unfortunately, despite their widespread use, the quality of clinical evidence supporting many of these products is variable and the most popular supplements are not necessarily the most effective.

"Awareness of the full range of treatment options available for osteoarthritis, and the evidence to support them, is essential for effective management" Dr Rod Hughes

Over-the counter options for OA joint pain: reviewing the latest evidence

Over-the-counter (OTC) products offer important additional options to individuals experiencing OA joint pain. This publication provides an overview of some of the latest evidence for the efficacy and safety of commonly-used OTC options for OA sufferers. The evidence presented here may help to inform healthcare professionals when advising patients with OA how to self-manage their condition.

Paracetamol

Paracetamol is an extremely common analgesic which has been available commercially since 1950. It has been widely reported that it accounted for 22.5 million primary care prescriptions in 2013 at a cost to the NHS of more than 80 million pounds[iv]. Paracetamol is currently a NICE-recommended first-line pharmacological treatment for OA that, until relatively recently, was considered safe and effective. In 2013, however, NICE announced that its advisors were "extremely concerned" over evidence of paracetamol's side-effects and that it would be recommending against its routine use in its updated guideline.

The 2013 NICE recommendations against routinely using paracetamol in OA were based on the following evidence:

- In a large prospective study in the US, individuals who frequently consumed paracetamol over a period of 12 years had a 35% increased risk of experiencing a major cardiovascular event (e.g. myocardial infarction, fatal coronary heart disease, stroke)[v].
- A UK study reviewing 1.2 million general practice records found a 28% increase in mortality with paracetamol use and a 50% increase when paracetamol was used in combination with ibuprofen compared with those not using either drug[vi]. The study also reported a 36% increase in the risk of upper gastrointestinal (GI) events, a 14% increase in heart attacks, and a 20% increase in the risk of renal failure with paracetamol use.
- A review of evidence by Osteoarthritis Research Society International (OARSI) for various analgesics in OA concluded that there was accumulating evidence to suggest that high-dose paracetamol may have upper GI side effects[vii]. The review also found some evidence to suggest a mild loss of renal function following the long-term consumption of high doses of paracetamol.
- In 2011, a group of researchers at Nottingham University reported an increased risk of haemoglobin reductions (indicating GI bleeding) after 13 weeks of treatment with ibuprofen and paracetamol alone, with the risk doubling when both drugs were taken in combination[viii].

Since the 2013 NICE announcement, several systematic reviews and meta-analyses[ix,x,xi] and new international guidelines[xii] have been published assessing the efficacy and safety of paracetamol in the treatment of OA. These have concluded that paracetamol provides minimal, if any, long-term pain relief in OA and is associated with considerable toxicity. The latest OARSI guidelines on the non-surgical management of knee OA suggest that paracetamol may be useful as a short-term analgesic, however, due to the risks associated with the drug – particularly when used for extended periods – conservative dosing and a treatment duration consistent with approved prescribing limits are recommended[xii].

Contributors' view

NICE guidelines are highly influential in the management of OA in primary care and it was unhelpful for NICE to suggest a blanket ban on paracetamol prescribing without offering alternative options or providing specific guidance on when and how paracetamol might be prescribed safely and appropriately. Evidence for the benefits of paracetamol in OA is weak and there appears to be good evidence of potential harm under certain circumstances. Until clearer guidance is issued by NICE, paracetamol should be used with caution in the long-term management of OA.

"One of the main reasons that paracetamol continues to be prescribed in OA is that it is inexpensive. The evidence base suggests that the risks may outweigh the benefits. It is going to take time to change practice, but I think that within 5 years, we will no longer be prescribing paracetamol for chronic pain relief"

Dr John Dickson

"If the use of paracetamol in OA is restricted, we need to offer patients safe and effective alternative treatment options. One of my major concerns is that despite paracetamol being one of the most prescribed drugs in General Practice, there are no recognised systems for monitoring the efficacy and safety of paracetamol and other analgesics"

Dr Martin Johnson

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in the treatment of OA when used both topically and orally. Topical NSAIDs are NICE-recommended first-line therapies that should be considered in addition to core treatments for people with OA of the knee or hand[i]. Oral NSAIDs are currently recommended only when paracetamol or topical NSAIDs do not provide adequate pain relief, with the lowest effective dose to be used for the shortest possible period of time[i].

Oral NSAIDs are associated with a broad spectrum of adverse events involving the liver, kidneys, cardiovascular system, skin and GI tract[xiii]. Gastrointestinal side-effects are the most common, ranging from dyspepsia, heartburn and abdominal pain to more serious events such as peptic ulcer with potentially life-threatening complications of bleeding and perforation[xiii]. In the treatment of OA, oral NSAIDs should generally be taken alongside a proton pump inhibitor (PPI) in order to minimise their GI side-effects[i].

Since publication of the partly-updated NICE guidelines in 2014, a comprehensive review of studies comparing the efficacy of oral ibuprofen and paracetamol in OA has been completed[xi]. This confirmed that ibuprofen is superior to paracetamol in terms of pain relief[xi]. Although safety was not the focus of this review, the authors drew on previous work demonstrating that ibuprofen use over two years was not associated with any cardiovascular risk or change in all-cause mortality, that the risk of upper GI bleeding with ibuprofen is lower than with all other NSAIDs, and that the risk with paracetamol appears to be greatest in doses above 2000 mg/day[xi]. The latest OARSI guidelines recommend both topical and oral NSAIDs for the treatment of OA of the knee[xii].

Contributors' view

NSAIDs such as ibuprofen are powerful anti-inflammatory drugs with a sound pharmacological basis for their efficacy in OA. Topical NSAIDs can provide good levels of pain relief for some people with hand or knee OA and are under-utilised in clinical practice. Oral NSAIDs may be taken intermittently, however, their long-term use is limited by significant toxicity issues and special care must be taken when using NSAIDs in the elderly and those with certain comorbidities. Anyone taking an oral NSAID to manage their OA should be monitored carefully by a healthcare professional.

"NSAIDs provide a good level of pain relief for some people with OA, but they must be used appropriately and patients should be reviewed at regular intervals due to their potentially extremely serious side effects"

Dr Rod Hughes

GOPO®

a key component of specially cultivated rose-hip (Rosa canina)

GOPO® is an anti-inflammatory compound derived from the seeds and husks of rosehips. GOPO® is produced using a unique manufacturing process that ensures product purity and maximises its joint health properties. GOPO® is the only rosehip derived compound to have been rigorously evaluated in randomised, controlled clinical trials.

Several randomised, double-blind, placebo-controlled studies evaluating the efficacy and safety of GOPO® in patients with OA have been completed[xiv,xv,xvi] and the quality of evidence for GOPO® in OA is considered to be good[xii]. These studies are summarised below:

- In the first study involving 100 patients with OA of the hip or knee[xiv], GOPO® 2.5g taken twice daily for 4 months significantly improved hip joint mobility compared with placebo. Pain also decreased significantly in the GOPO® treatment group compared with the placebo treatment group. In this study, 64% of patients reported at least some reduction of pain while receiving GOPO® treatment.
- A second study including 112 patients with OA in various joints[xv] reported that 3 months of GOPO® treatment at a dose of 5g/day significantly improved morning pain and stiffness and significantly improved mood, sleep quality, energy and well-being. GOPO® also reduced the need for rescue medications such as tramadol, codeine, paracetamol and aspirin.
- In a third study involving 94 patients with OA of the hip of knee[xvi], eight out of 10 patients reported a significant reduction in pain compared with placebo after 3 weeks of GOPO® (5g/day). After 3 months of treatment, disability, joint stiffness and global assessments of disease severity all improved significantly in the GOPO® treatment group compared with the placebo group. The consumption of rescue medications significantly declined with GOPO® treatment.
- A meta-analysis of data from these three randomised, controlled studies confirmed that GOPO® offers significant and robust joint pain relief, enabling a reduction in the consumption of rescue medications[xvii]. A comparison of pain effect size scores in these studies with those published for paracetamol and glucosamine suggests that GOPO® may be more effective than either of these two treatments[xvii].

There is additional preclinical evidence that GOPO® may protect joint cartilage by modulating cytokine and chemokine expression[xviii].

Contributors' view

The current evidence base suggests that, with an estimated number needed to treat (NNT) of 5, GOPO® represents a promising option for OA with significant anti-inflammatory and clinical benefits. The studies – although relatively small – are well conducted and the treatment appears to be effective and well tolerated. If OA patients are interested in taking a joint supplement for their OA, a 3-month trial of GOPO® could be of benefit.

"We now know that Osteoarthritis is an inflammatory condition, rather than simply being attributable to 'wear and tear', therefore the anti-inflammatory effects of GOPO® may be of benefit"

Dr Rod Hughes

"A three month trial of GOPO® is certainly worthwhile and I recommend patients go and talk to their pharmacist"

Dr John Dickson

Glucosamine and chondroitin

Glucosamine and chondroitin are popular joint health supplements that are available individually or in combination products. Glucosamine is a substance found naturally in the human body and is used by the body as one of the building blocks of joint structures including cartilage, ligaments, tendons and synovial fluid. Chondroitin is also found naturally in the body and is an essential component of cartilage.

NICE has conducted a thorough review of the evidence supporting the use of glucosamine, chondroitin and their combination and concluded that they should not be prescribed for the treatment of OA by healthcare professionals[i]. Similar conclusions have been drawn in the recent OARSI guidelines[xii]. Both supplements have also been reviewed by The Cochrane Collaboration[xix,xx], the findings of which are summarised below:

Glucosamine[xix]

- In a review of 25 randomised controlled trials (RCTs), the high quality studies reported no difference between glucosamine and placebo in terms of pain improvement.
- No consistent improvement in function was reported in the high quality studies of glucosamine relative to placebo.
- In studies assessing the Rotta brand of glucosamine (including low quality and older studies), glucosamine was superior to placebo in terms of pain and functional improvements.
- The number of study participants reporting adverse events was similar in glucosamine- and placebo-treated individuals.

Chondroitin[xx]

In a review of 43 RCTs – most of which were of low quality – chondroitin was reported to be better than placebo at improving pain in short-term studies (<6 months). The benefit was considered small to moderate (i.e. an 8-point greater improvement in pain on a pain scale of 0 to 100 after 6 months).

- Chondroitin was well tolerated in these studies.

Contributors' view

Although the clinical trial evidence supporting the use of glucosamine and chondroitin is relatively weak, many individuals believe they benefit from taking these supplements. The marginal benefits observed in randomised controlled trials do not support them being prescribed in the NHS, however, OA sufferers should not be discouraged from trying these supplements as some may gain meaningful symptom relief.

"Overall the efficacy of glucosamine is only marginal, and the prescription costs to the NHS are extremely high"

Dr John Dickson

"In my experience glucosamine is often recommended by HCP's despite it not being advised by NICE, I would suggest this practice is reviewed in view of the lack of strong supporting clinical data"

Dr Martin Johnson

Omega-3 (fish oil) supplements

Fish oil supplements are popular among patients with OA although their effectiveness and precise benefits are still debated. Fish oils are rich in omega-3 fatty acids, which have strong anti-inflammatory properties and may also play a role in lowering cholesterol and triglyceride levels. Most fish oil research has been conducted in patients with rheumatoid arthritis (RA), with studies showing consistently that daily fish oil supplements reduce the use of other medications and improve joint pain[xxi].

Evidence for the benefits of fish oil in OA patients is scarce, but has been reviewed recently[xxi]. According to these reviewers, only six studies have addressed this topic and their endpoints and results were inconsistent[xxi]. Two studies are particularly noteworthy, although both have major limitations[xxi].

- In the first clinical study of omega-3 supplementation in OA, which was conducted in 1992, researchers compared 10g of cod liver oil with 10g of olive oil[xxii], both taken daily over 24 weeks by 86 patients with OA. No significant difference was found between the two treatment groups in terms of changes in pain and disability. Both treatments failed to significantly reduce these endpoints.
- Another study compared the effects of glucosamine with and without omega-3 fatty acids in 182 patients with knee or hip OA and reported >90% reductions in morning stiffness and pain with the combination of fish oil and glucosamine[xxiii]. The design and reporting of this study have been strongly criticised[xxi].

Thus, despite the popularity of fish oil supplements and the assumption of benefit based on the RA literature, there is insufficient clinical evidence to justify the use of fish oils in the treatment or prevention of OA[xxi].

Contributors' view

RA has a much more severe inflammatory component than OA. Omega-3 (fish oil) supplements have a wide range of health benefits and effectively relieve the symptoms of RA for many people. Unfortunately, there is no good quality evidence that these supplements work in OA and they should not be recommended as an OTC treatment for this condition.

"Despite being popular with joint pain sufferers, the evidence for the benefit of Omega 3 in OA is very limited. However, sufferers of RA are expected to see greater benefit"

Dr Martin Johnson

The importance of lifestyle interventions

Although it is outside the scope of this publication, it is important to recognise that lifestyle interventions play a key role in the management of OA joint pain. According to NICE, everyone with OA should have an individualised self-management plan that encourages positive behavioural changes such as exercise, weight loss, use of suitable footwear and pacing[i].

An extensive evidence base exists supporting the use of muscle strengthening and aerobic exercises to reduce pain, disability, medication intake and improve physical functioning and well-being in OA, and exercise is a considered a core OA treatment[i]. Published data also suggests that weight loss in people with OA who are overweight reduces excessive mechanical loading of the joints, leading to improved function and potentially reducing joint pain[i].

For further information about osteoarthritis and lifestyle interventions in the management of OA, the reader is directed to the following sources:

NHS Choices

www.nhs.uk/Conditions/Osteoarthritis/Pages/Introduction.aspx

www.nhs.uk/Conditions/Osteoarthritis/Pages/treatment.aspx

Arthritis Research UK

www.arthritisresearchuk.org/arthritis-information/conditions/osteoarthritis

Patient

www.patient.info/jointpainhub

Consensus and practical steps to improving the management of OA

This publication provides an overview of some of the latest clinical evidence supporting or refuting the benefits of many of the most popular OTC products used by people with OA.

Based on this review, the following may help to improve the management of OA in the future:

- When advising on the options for managing OA joint pain, healthcare professionals should take a holistic approach and consider discussing both lifestyle interventions and evidence-based OTC analgesics and nutritional supplements.
- Part of the evaluation of OA should be concerned with an assessment of the patients' pain (which has been recently reinforced in the NICE OA Quality Standards).
- Until further specific guidance is forthcoming, paracetamol should be used with caution in the management of OA, bearing in mind that the evidence does not support its efficacy over the long-term, and safety issues have emerged when paracetamol is used in large doses for prolonged periods of time.
- Topical NSAIDs are effective in hand and knee OA and should be considered as they are likely to be safer and have fewer side effects than oral preparations, especially oral NSAIDs. Oral ibuprofen appears to be associated with fewer adverse consequences than other oral NSAIDs; however, patients taking ibuprofen should be monitored carefully by a healthcare professional.
- A 3-month trial of GOPO® could be considered if OA sufferers are seeking a non-prescription option for their joint pain. GOPO® is emerging as a safe and effective natural health supplement with good quality evidence for its benefits in OA.
- Glucosamine and chondroitin are popular and anecdotal evidence suggests they may work for certain individuals, however the clinical evidence for their benefits is inconsistent and they are not currently recommended by NICE.
- Fish oils containing omega-3 do not appear to be as effective for people with OA as they are for those with RA and cannot be recommended based on current evidence.

"If patients continue to experience unacceptable symptoms after a 3-month trial of a new treatment, it's time to move on and try something different. This is an important concept when developing a self-management strategy"

Dr John Dickson

"It is important to consider a range of treatment options outside of simply prescribing paracetamol, and a holistic approach is absolutely key"

Dr Rod Hughes

"Broadening awareness of the range of management options for OA, including nutraceuticals and the evidence base to support, them should be a priority for health care professionals treating the disease"

Dr Martin Johnson

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