SICOT

(International Society of Orthopaedic Surgery and Traumatology)

Current Concepts in the Management of Osteoarthritis

Module 1

The Epidemiology, Etiology, Diagnosis, and Treatment of Osteoarthritis of the Knee

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The Epidemiology, Etiology, Diagnosis, and Treatment of Osteoarthritis of the Knee

Contents

SYLLABUS

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The Burden of Pain Associated with Osteoarthritis in the Hip or Knee from the Patient's Perspective: A Multinational Cross-Sectional Study

ABSTRACT :

Introduction: To evaluate, from the patient's perspective, the burden of pain associated with hip/knee osteoarthritis (OA) in the USA and selected European Union (EU) countries.

Methods: Data were drawn from the 2017 global Adelphi OA Disease Specific ProgrammeTM (DSP). Patients with hip/knee OA were stratified based on pain intensity and the presence/absence of current opioid use. Outcomes included Western Ontario and McMaster Universities Osteoarthritis Index scores, functional limitations, unmet treatment needs, Charlson Comorbidity Index, relevant comorbid conditions, the 5-dimension 5-level EuroQol, and the Work Productivity and Activity Impairment

Results: The study population comprised 2170 patients (US: n = 623 [28.7%]; EU: n = 1547 [71.3%]) with knee (54.9%), hip (24.6%), or knee/hip (20.5%) OA. Mean (SD) age was 66.4 (11.2) years. Patients had no/mild pain without opioid use (39.6%), no/mild pain with opioid use (10.2%), moderate/severe pain without opioid use (30.6%), and moderate/severe pain with opioid use (19.7%). Compared with the reference group, patients with moderate/severe pain reported significantly (p\0.05) higher functional limitations, greater use of C 3 treatments and treatment dissatisfaction, reduced quality of life, and impaired work productivity and activity. The burden was highest with moderate/severe pain with opioid use. Results were generally similar in the US and E cohorts.

Conclusions: The results from this multinational cross-sectional study indicate that the impact of OA pain is multidimensional, worsened by increasing pain intensity, and may not be adequately addressed by current treatment strategies.

Keywords: Comorbidity; Daily activity; Healthrelated quality of life; Opioid; Osteoarthritis; Pain; Physical functioning; Work productivity.

INTRODUCTION

Osteoarthritis (OA) is a chronic joint disease that represents a major global public health problem [1,2]. Affecting more than 300 million adults globally [2], OA is the most common form of arthritis and a leading cause of disability [1]. Although OA can involve any synovial joint [1], the most commonly affected sites are the hips, knees, and hands [2]. Risk factors for OA include joint injury, increasing age, female sex, obesity, and predisposing genetic factors [3]. An aging population and increased rates of obesity are contributing to the growing incidence of OA [1]. OA can be defined in terms of radiologic changes as well as symptoms, although there may be a discordance between these findings, with some patients having radiologic findings without symptoms [4]. Pain is the disease characteristic that most often drives patients to seek medical attention [4], and it negatively affects multiple aspects of a patient's life, including mobility, sleep, mood, and healthrelated quality of life (HRQoL) [5]. OA is also associated with a substantial economic burden [4,6]. Although there is no cure for OA, a variety of therapies are available for OA pain, including non-pharmacologic approaches (e.g., physical therapy and weight management) and pharmacologic agents (e.g., acetaminophen [paracetamol], nonsteroidal anti-inflammatory drugs [NSAIDs], and opioids) [7]. Opioids have been traditionally recommended as options for OA pain [8,9] and are still being prescribed in some patients [10]. However, use of opioids to manage OA pain remains controversial. Results from randomized controlled trials (RCTs) demonstrated that opioids provide few benefits relative to other analgesics for relieving OA pain [11–14]. Furthermore, opioids are associated with a number of safety concerns, including toxicities and the risk of abuse and dependency [15–17]. Conseqeuntly, the recently updated guidelines from the Osteoarthritis Research Society International (OARSI) strongly recommend against opioid use for OA pain [18]. In addition, the most recent guidelines from the American College of Rheumatology (ACR)/Arthritis Foundation (AF) conditionally recommend against the use of opioids in patients with OA, acknowledging that these agents may be used after exhausting other treatment options [19].

The objective of this multinational crosssectional study was to evaluate the burden of pain associated with OA in the hip and/or knee from the perspective of adult patients in the US and selected countries in the European Union (EU). In this study, patients with hip/knee OA were stratified based on pain intensity and the presence/absence of current opioid use. Given that OA exerts multiple effects on patients' lives, this study examined a spectrum of measures of disease burden, including functional

burden, unmet treatment needs, comorbidity burden, HRQoL, work productivity, and daily activity.

METHODS

Study Design

This study utilized data from the Adelphi Disease Specific Programme (DSP)TM, which is a large, multinational, observational study designed to capture a cross-section of real-world data for a range of common chronic diseases [20]. This study used de-identified, aggregated patient data and was granted exceptions from requiring ethics approval. Patients provided consent to participate. Data were collected in clinical practice settings by physicians who provided relevant information on consecutive patients consulting for the disease of interest.

Patients were invited to participate by completing an independent questionnaire. Data were drawn from the 2017 global Adelphi OA DSP, which surveyed primary care physicians, rheumatologists, orthopedists, and their patients with OA during their regular office visits. Physician and patient data were collected at the same time. Participating physicians and patients were each assigned a study number to aid anonymous data collection and to allow linkage of data during data collection and analysis. This study included patients from the US and the five most populated EU countries at the time of the analysis (Germany, France, UK, Italy, and Spain [21]) who were diagnosed with OA of the knee and/or hip by their consulting physicians. For each included patient, during the visits physicians completed a patient record form on the patient's history of OA treatment regimens, current use of opioids and other treatments for OA pain, and comorbidities. Patients who agreed to participate completed a self-assessment form that included quetions and validated measures for evaluating disease burden. OA pain intensity in the past 48 h was measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Numerical Rating Scale (NRS) 3.1, a widely used, validated, self-administered, disease-specific questionnaire [22,23]. Using the pain component of the WOMAC, patients were stratified by no/mild pain (score 0–3) and moderate/severe pain (score 4–10) and at the same time by the presence or absence of current opioid use, resulting in four groups: no/mild pain without current opioid use; no/mild pain with current opioid use; moderate/severe pain without current opioid use; moderate/severe pain with current opioid use.

Outcome Measures

Outcomes included measures for physical functioning, unmet treatment needs, comorbidity, HRQoL, and work productivity and daily activity. Physical functioning was reported by patients using physical function and stiffness scores from the WOMAC NRS 3.1, which are scored on a range from 0 to 10, with higher scores indicating a worse condition over the past 48 h [22,23]. Physical functioning was also assessed by patient responses to stand-alone questions related to functional limitations ("Has your mobility been impacted due to your OA?" "Do you need an aid to get around, either inside or outside of your house due to your OA?" "Do you need anyone to help you with any daily activities or tasks?" "Have you ever suffered a fall inside or outside of your home that you believe was because of your OA?"); these questions were not previously validated. Unmet treatment needs were measured by the use of C 3 treatment regimens for OA and patient-reported dissatisfaction with treatment. Comorbidity burden was evaluated by the physician using the Charlson Comorbidity Index (CCI) [24]. To further examine relevant comorbidities, rates of any cardiovascular condition, hypertension, depression or anxiety, osteoporosis, and chronic low back pain were recorded by the physician.

HRQoL was measured using the 5-dimension, 5-level EuroQol (EQ-5D-5L), a generic, patient-reported measure of health status [25]. The EQ-5D-5L consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with five levels of impairment responses, and a health state visual analog scale (VAS; 0 = worst health state, 100 = best health state). Patient responses on the five dimensions are used to generate a utility index that represents a health state with anchors at 0 (death) and 1 (perfect health), although index scores\0 are possible. For the EQ-5D-5L utility index, individual country value sets were used for the US and EU countries. The minimally important difference (MID) for the EQ-5D-5L utility index is estimated to be a difference of[0.037 to 0.069 points [26].

Work productivity and daily activity over the

Key points

Why carry out this study?

- Osteoarthritis (OA) is a chronic joint disease that represents a major global public health problem; pain is the main symptom of OA and the disease characteristic that most often drives patients to seek medical attention.
- The objective of this cross-sectional study was to evaluate the burden of pain associated with knee, hip, or knee and hip OA from the perspective of adult patients in the USA and selected countries in the European Union (EU).

What was learned from the study?

- Of 2170 patients with OA, those with moderate/severe pain reported significant burdens that affected multiple aspects of their lives.
- The burdens were higher among patients with moderate/severe pain versus no/mild pain and among patients with current opioid use versus patients without current opioid use, regardless of pain intensity.
- These results indicate that the multidimensional impact of OA pain is worsened by increasing pain intensity and may not be adequately addressed by opioid therapy, underscoring the need for alternative therapeutic agents for the management of knee/hip OA pain.

Key points

- Osteoarthritis (OA) is a chronic joint disease that represents a major global public health problem. Affecting more than 300 million adults globally, OA is the most common form of arthritis and a leading cause of disability. Although OA can involve any synovial joint, the most commonly affected sites are the hips, knees, and hands. Risk factors for OA include:
- Joint injury
- Increasing age
- Female sex
- Obesity
- Predisposing genetic factor
- An aging population and increased rates of obesity are contributing to the growing incidence of OA. OA can be defined in terms of radiologic changes as well as symptoms, although there may be a discordance between these findings, with some patients having radiologic findings without symptoms.

past 7 days were assessed using the patient-reported Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) version 2.0, with OA as the specified disease [27]. Activity impairment was assessed among all patients; work productivity was assessed among employed patients only.Assessed WPAI:SHP scales were impairment while working due to problem ("presenteeism"), work time missed ("absenteeism"), overall work impairment, and activity impairment.

Statistical Analysis

STATA v16.0 software was used in the statistical analysis. Bivariate testing was used to compare outcomes for patients with no/ mild pain without current opioid use versus those with no/ mild pain with current opioid use, moderate/ severe pain without current opioid use, and moderate/severe pain with current opioid use. Statistical significance was set at p\0.05.

RESULTS

Patient Characteristics

The study sample comprised 2170 patients with OA of the knee and/or hip from the 2017 global Adelphi OA DSP (Table 1). The mean age was 66.4 years, 57.9% of patients were female, and 88.4% were white or Caucasian. OA was reported in the knee (without hip), hip (without knee), or both hip and knee in 54.9%, 24.6%, and 20.5% of patients, respectively (OA may have been present in joints other than the knee or hip). Participating patients were from the US (n = 623; 28.7%) and EU (n = 1547; 71.3%).

Among the study sample, 1090 patients (50.2%) had moderate/severe pain and 648 patients (29.9%) were currently receiving opioids. Despite current opioid treatment, 427 of the 648 patients (65.9%) still reported moderate/ severe pain. Based on pain severity and opioid use, patients were grouped into four categories: 859 patients (39.6%) had no/mild pain without opioid use, 221 patients (10.2%) had no/mild pain with opioid use, 663 patients (30.6%) had moderate/severe pain without opioid use, and 427 patients (19.7%) had moderate/ severe pain with opioid use (Supplementary Fig. 1). Demographic and clinical characteristics were generally consistent across the four categories, although patients with moderate/severe pain with opioid use were older, had a higher proportion of females, had a higher incidence of OA affecting both the knee and hip, and had a higher incidence of obesity (Table 1). Moderate/ severe pain was reported by 248 of 623 US patients (39.8%) and 842 of 1547 EU patients (54.4%), and opioids were used by 141 US patients (22.6%) and 507 EU patients (32.8%; Supplementary Fig. 1). Opioids were used by 46.1% of patients in Spain, 39.8% of patients in the UK, 29.7% of patients in Italy, 27.4% of patients in Germany, and 25.5% of patients in France (Supplementary Fig. 2). Despite receiving opioids, 93 patients (14.9%) in the US cohort and 334 patients (21.6%) in the EU cohort still reported moderate/severe pain (Supplementary Fig. 1). The proportion of patients with moderate/ severe pain and opioid use was 33.3% in Spain, 25.7% in the UK, 23.9% in Italy, 16.7% in France, and 15.0% in Germany (Supplementary Fig. 2).

Among current opioid users (n = 648) in the total population, 463 patients (71.5%) used weak opioids (e.g., codeine, hydrocodone, or tramadol), 171 patients (26.4%) used strong opioids (e.g., morphine, hydromorphone, or oxycodone), and 14 patients (2.2%) used weak and strong opioids in combination (Supplementary Fig. 3). In the total population, strong opioids were used more frequently in patients with moderate/ severe pain than in those with no/mild pain (29.0% versus 21.3%). Strong opioids were used most frequently in Germany (53.9%), followed by Italy (39.1%), Spain (32.6%), the US (13.5%), France (11.5%), and the UK (8.3%) (Supplementary Fig. 4).

Physical Functioning

In the total population, patients with moderate/ severe pain reported higher scores in WOMAC physical function and stiffness than patients with no/mild pain, which was indicative of higher functional impairment (Fig. 1). In addition, patients with opioid use reported more physical function limitations than those without opioid use at the same pain level (i.e., patients with no/mild pain with opioid use had more limitations than those with no/mild pain without opioid use, as did patients with moderate/ severe pain with opioid use versus those without opioid use; Fig. 1a). Patients with moderate/ severe pain with opioid use experienced the most limitations in physical function and joint stiffness. WOMAC physical function

Table 1 Characteristics of patients with hip and/or knee OA in the total population (US and EU cohorts; = 2170) by pain intensity and opioid use

	Total (N = 2170)	No/mild pain without opioid use (n = 859)	No/mild pain with opioid use (n = 221)	Moderate/severe pain without opioid use (n = 663)	Moderate/severe pain with opioid use (n = 427)
Age					
No	2170	859	221[c]	663[c]	427[c]
Mean (SD),[a] years	66.4 (11.2)	64.5 (10.9)	68.0 (9.7)	66.2 (11.6)	69.8 (10.8)
Sex					
No	2170	859	221	663[c]	427[c]
Male	914 (42.1)	389 (45.3)	101 (45.7)	266 (40.1)	158 (37.0)
Female	1256 (57.9)	470 (54.7)	120 (54.3)	397 (59.9)	269 (63.0)
Race/ethnicity					
No	2170	859	221	663	427[c]
White/Caucasian	1919 (88.4)	747 (87.0)	204 (92.3)	604 (91.1)	364 (85.2)
Hispanic/Latino	88 (4.1)	31 (3.6)	6 (2.7)	22 (3.3)	29 (6.8)
African American	72 (3.3)	41 (4.8)	6 (2.7)	13 (2.0)	12 (2.8)
Others	91 (4.2)	40 (4.7)	5 (2.3)	24 (3.6)	22 (5.2)
Country					
No	2170	859	221[c]	663[c]	427[c]
US	623 (28.7)	327 (38.1)	48 (21.7)	155 (23.4)	93 (21.8)
Germany	468 (21.6)	178 (20.7)	58 (26.2)	162 (24.4)	70 (16.4)
France	377 (17.4)	153 (17.8)	33 (14.9)	128 (19.3)	63 (14.8)
Spain	306 (14.1)	77 (9.0)	39 (17.6)	88 (13.3)	102 (23.9)
UK	241 (11.1)	78 (9.1)	34 (15.4)	67 (10.1)	62 (14.5)
Italy	155 (7.1)	46 (5.4)	9 (4.1)	63 (9.5)	37 (8.7)
Site of OA[b]					
No	2170	859	221[c]	663	427[c]
Knee (without hip)	1192 (54.9)	516 (60.1)	102 (46.2)	371 (56.0)	203 (47.5)
Hip (without knee)	533 (24.6)	183 (21.3)	73 (33.0)	167 (25.2)	110 (25.8)
Both knee and hip	445 (20.5)	160 (18.6)	46 (20.8)	125 (18.9)	114 (26.7)
BMI					
No	2169	859	221	662	427[c]
Mean (SD), kg/m^2	28.1 (5.2)	27.7 (4.8)	28.0 (4.9)	28.0 (5.2)	29.2 (5.7)
Obese (BMI [30 kg/m^2)	641 (29.6)	221 (25.7)	65 (29.4)	189 (28.5)	166 (38.9)

Table 1 continued

	Total (N = 2170)	No/mild pain without opioid use (n = 859)	No/mild pain with opioid use (n = 221)	Moderate/severe pain without opioid use (n = 663)	Moderate/severe pain with opioid use (n = 427)
Employment status					
No	2150	849	217	658[c]	426[c]
Working full-time	545 (25.3)	286 (33.7)	46 (21.2)	157 (23.9)	56 (13.1)
Working part-time	124 (5.8)	54 (6.4)	6 (2.8)	43 (6.5)	21 (4.9)
On long-term sick leave	17 (0.8)	2 (0.2)	0	5 (0.8)	10 (2.3)
Homemaker	256 (11.9)	93 (11.0)	26 (12.0)	72 (10.9)	65 (15.3)
Student	2 (0.1)	0	0	2 (0.3)	0
Retired	1156 (53.8)	406 (47.8)	136 (62.7)	364 (55.3)	250 (58.7)
Unemployed	50 (2.3)	8 (0.9)	3 (1.4)	15 (2.3)	24 (5.6)

Values are the number (%), unless indicated otherwise
BMI body mass index, EU European Union,OA osteoarthritis, SD standard deviation
[a] Patients aged 90 years were coded as being 90 years of age
[b] OA may have been present in joints other than the knee or hip
[c] p\ 0.05 compared with patients with no/mild pain without opioid use

Key points

- Opioids have been traditionally recommended as options for OA pain and are still being prescribed in some patients. However, use of opioids to manage OA pain remains controversial. Results from randomized controlled trials (RCTs) demonstrated that opioids provide few benefits relative to other analgesics for relieving OA pain. Furthermore, opioids are associated with a number of safety concerns, including toxicities and the risk of abuse and dependency.

and stiffness scores were more than twofold higher among patients with moderate/severe pain with or without opioid use compared with those with no/mild pain without opioid use (6.3 and 5.7 versus 2.5 [p\0.05] and 6.3 and 5.7 versus 2.7 [p\0.05], respectively). Patterns were similar in the US and EU cohorts (Fig. 1).

Higher rates of mobility limitation, need for a walking aid, need for help with daily activities, and suffering a fall were noted with moderate/ severe pain than with no/mild pain (Table 2). Similarly, the prevalence of these limitations was higher among those with opioid use relative to those without opioid use at the same pain level (Table 2). These burdens were highest in patients with moderate/severe pain with opioid use and when compared with those with no/mild pain without opioid use showed more than a twofold higher need of a walking aid (67.3% versus 30.0%; p\0.05), almost a fivefold higher need for help with daily activities (48.9% versus 10.2%; p\0.05), and more than a twofold higher fall rate (45.3% versus 17.6%; p\0.05). Patterns for functional burdens were similar in the US and EU cohorts (Supplementary Tables 1 and 2).

Treatment Needs

Treatment needs (i.e., the requirement for three or more treatment regimens for OA pain or dissatisfaction with treatment) were higher with moderate/severe pain than with no/mild pain and with opioid use than with no opioid use at the same pain level (Table 2). Patients with moderate/severe pain with opioid use reported the greatest treatment needs. Among patients with moderate/severe pain with opioid use in the total population, approximately half (50.1%) reported using three or more treatment regimens for OA pain and more than one-third (38.1%) reported being dissatisfied with their treatment. Patterns in treatment needs were similar across the US and EU cohorts (Supplementary Tables 1 and 2).

Comorbidity

In the total population, the mean CCI score was approximately twofold higher among

patients with current opioid use than those without opioid use at the same severity level (Fig. 2). Patients with moderate/severe pain with opioid use had the highest mean CCI score, which was significantly higher than those with no/mild pain without opioid use (0.74 versus 0.30, respectively; p\0.05; Fig. 2). These trends were also observed in the US and EU cohorts.

Relevant comorbid conditions were more prevalent among patients with moderate/ severe pain than among those with no/mild pain, as well as among patients with opioid use than among those with no opioid use at the same pain level (Table 2). Patients with moderate/ severe pain with opioid use had the highest rates of comorbid conditions. Rates of depression or anxiety, osteoporosis, and chronic low back pain were more than twofold higher among patients with moderate/severe pain with opioid use compared with those with no/mild pain without opioid use (p\0.05). The majority of patients with moderate/severe pain with zopioid use had been diagnosed with any cardiovascular condition (72.1%) or hypertension (66.3%); more than one-third of these patients (34.4%) suffered from anxiety or depression. Rates of comorbidities were slightly higher in the US than in the EU cohort, although trends were similar between the two cohorts (Supplementary Tables 1 and 2).

HRQoL

HRQoL, as assessed by the EQ-5D-5L VAS and index scores, was lower among patients with moderate/severe pain than among those with no/mild pain as well as among those with opioid use than among those with no opioid use at the same pain level (Fig. 3). Differences in EQ- 5D-5L index scores between patients with no/ mild pain without opioid use and patients in the other three study groups were clinically relevant (i.e., exceeding the estimated MID of 0.037 [25]). Patients with moderate/severe pain with opioid use reported the poorest HRQoL. Mean EQ-5D-5L VAS and index scores were significantly lower among patients with moderate/ severe pain with or without opioid use than among those with no/mild pain without opioids (p\0.05). EQ-5D-5L VAS and utility index scores were slightly lower in the EU cohort than in the US cohort, although overall trends were similar.

Work Productivity and Daily Activity

In the total population, patients with moderate/ severe pain reported greater percentages of work time missed due to problem (absenteeism; Fig. 4a), impairment while working due to problem (presenteeism; Fig. 4b), overall work impairment (Fig. 4c), and activity impairment (Fig. 4d) than patients with no/mild pain, as assessed by the WPAI:SHP. In addition, patients with opioid use generally reported greater percentage impairment on all WPAI:SHP scales than those without opioid use, regardless of pain level. The percentage of impairment due to presenteeism (Fig. 4b) exceeded that of absenteeism (Fig. 4a), regardless of pain level or opioid use.

In the total population, the greatest percentage impairment in WPAI:SHP scales was reported by patients with moderate/severe pain with opioid use. Patients with moderate/severe pain with or without opioid use, compared with those with no/mild pain without opioid use, reported significantly greater work productivity and daily activity impairment (p\0.05; Fig. 4). Across WPAI:SHP scales, reported impairment was more than twofold higher in patients with moderate/severe pain with opioid use compared with those with no/mild pain without opioid use. WPAI:SHP results were generally consistent across US and EU cohorts. However, among patients with moderate/ severe pain with opioid use, the percentage of overall work impairment was substantially greater in the EU cohort than in the US cohort (60.9% versus 41.8%; Fig. 4c), and absenteeism was more evident in the EU cohort than in the US cohort (Fig. 4a).

DISCUSSION

In this cross-sectional study, patients from the US and five EU countries with moderate/ severe OA pain, regardless of opioid use,r ported significant burdens that encompassed reductions in physical functioning, greater treatment needs, more comorbidities, reduced HRQoL, and impairments in work productivity and daily activities. The burdens were also generally higher among patients with current opioid use compared with those without current opioid use, regardless of pain intensity; patterns were generally similar across US and EU cohorts.
Among the total study population, approx-

Key points

- Treatment needs (i.e., the requirement for three or more treatment regimens for OA pain or dissatisfaction with treatment) were higher with moderate/severe pain than with no/ mild pain and with opioid use than with no opioid use at the same pain level.
- Patients with moderate/severe pain with opioid use reported the greatest treatment needs. Among patients with moderate/ severe pain with opioid use in the total population, approximately half (50.1%) reported using three or more treatment regimens for OA pain and more than one-third (38.1%) reported being dissatisfied with their treatment.

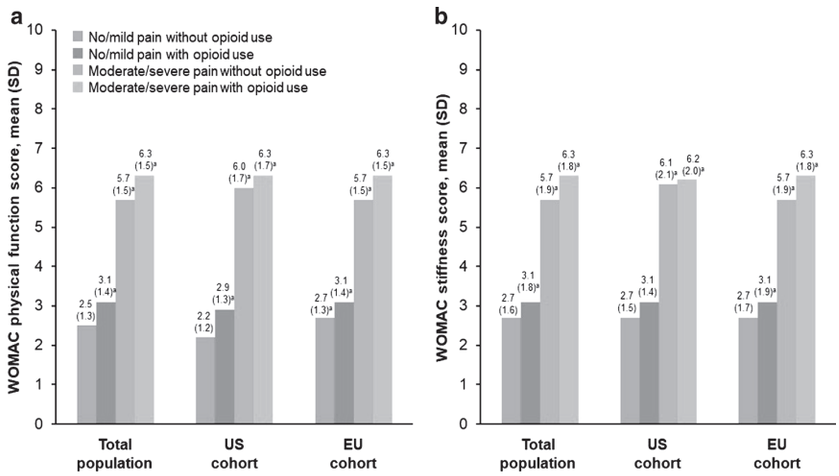

Fig. 1 WOMAC scores in patients with hip and/or knee OA by pain intensity and opioid usePhysical function scores.b Stiffness scores. Scale ranges from 0 to 10, with higher scores indicating worse condition. 0.05 versus no/mild pain without opioid use. European Union, OA osteoarthritis, SD standard deviation,WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

Key points

- In this cross-sectional study, patients from the US and five EU countries with moderate/severe OA pain, regardless of opioid use, reported significant burdens that encompassed reductions in:
- Physical Functioning
- Greater Treatment Needs
- More Comorbidities
- Reduced HRQoL
- Impairments In Work Pro ductivity
- Daily Activities
- The burdens were also generally higher among patients with current opioid use compared with those without current opioid use, regardless of pain intensity; patterns were generally similar across US and EU cohorts.

imately half of patients with OA had moderate/ severe pain, almost a third were currently receiving opioids, and approximately one-fifth still reported moderate/severe pain despite current opioid use.

OA is associated with a significant functional burden that can result in disability [4,5]; not surprisingly, the results from this study demonstrated greater functional impacts with higher pain intensity. Patients with moderate/ severe pain were more likely than patients with no/mild pain to report impairment in physical function and stiffness, sp cific needs such as for a walking aid or help with daily activities, and that they suffered a fall. These results are consistent with evidence showing that pain is a major contributing factor to the functional limitations associated with OA [4].

The results from this study also demonstrated greater functional impacts among patients with OA pain using opioids. Patients using opioids reported more physical fun tional limitations than those not using opioids at the same pain level. These results suggest that opioids provided no benefit in some patients and may have even contributed to worse functional outcomes. The increased frequency of physical functional limitations, use of a walking aid, and falls with opioid use may potentially be related to opioid-related adverse events, specifically dizziness and somnolence. The results of this study also revealed greater unmet treatment needs among patients treated with opioids. In particular, more than half of patients with moderate/severe pain with opioid use reported using three or more treatment regimens for OA, possibly indicating the lack of efficacy with one or two regimens. Additionally, more than onethird of these patients reported treatment dissa isfaction, suggesting that management with opioids may not adequately address OA pain. Treatment dissatisfaction with opioids may be related to the toxicity and low efficacy in OA that are well-recognized issues associated with this drug class. These results are consistent with those from RCTs showing that opioids provide limited benefit to patients with OA pain [11–14] and suppor the recently updated OARSI and ACR/AF guidelines, which strongly recommend against the use of opioids for managing OA pain [18,19].

The results of this study confirm previous work showing high comorbidity among patients with OA [28–31] and further revealed that patients with higher pain intensity with current opioid use have the greatest level of comorbidity. Mean CCI scores were approx-

Table 2 Burdens in patients with hip and/or knee OA in the total population (US and EU cohorts; intensity and opioid use

	No/mild pain without opioid use (n = 859)	No/mild pain with opioid use (n = 221)	Moderate/severe pain without opioid use (n = 663)	Moderate/severe pain with opioid use (n = 427)
Physical function				
Mobility limitation (n = 2094)	432 (52.4)	149 (69.0)	498 (78.2)[c]	362 (87.0)[c]
Need for walking aid (n = 1427)	129 (30.0)	67 (45.3)	225 (46.1)[c]	243 (67.3)[c]
Need for help with daily activities (n = 2059)	83 (10.2)	46 (21.4)	183 (29.3)[c]	197 (48.9)[c]
Suffered a fall (n = 2115)	148 (17.6)	47 (21.7)	195 (30.6)[c]	189 (45.3)[c]
Treatment needs				
Use of C 3 treatment regimens for OA (n = 1965)	102 (13.9)	90 (40.7)	132 (22.7)	214 (50.1)[c]
Dissatisfaction with treatment (n = 1859)	40 (5.8)	22 (10.6)	144 (25.5)[c]	153 (38.1)[c]
Comorbidity (N = 2170)				
Any cardiovascular condition	421 (49.0)	151 (68.3)	379 (57.2)[c]	308 (72.1)[c]
Hypertension	388 (45.2)	142 (64.3)	355 (53.5)[c]	283 (66.3)[c]
Depression or anxiety	129 (15.0)	49 (22.2)	146 (22.0)[c]	147 (34.4)[c]
Osteoporosis	51 (5.9)	22 (10.0)	67 (10.1)[c]	65 (15.2)[c]
Chronic low back pain	52 (6.1)	25 (11.3)	85 (12.8)[c]	93 (21.8)[c]

Values are the number (%)
EU European Union,OA osteoarthritis
[a] Among those who reported mobility limitation
[b] Among those currently treated
[c] p\ 0.05 versus no/mild pain and no opioid use

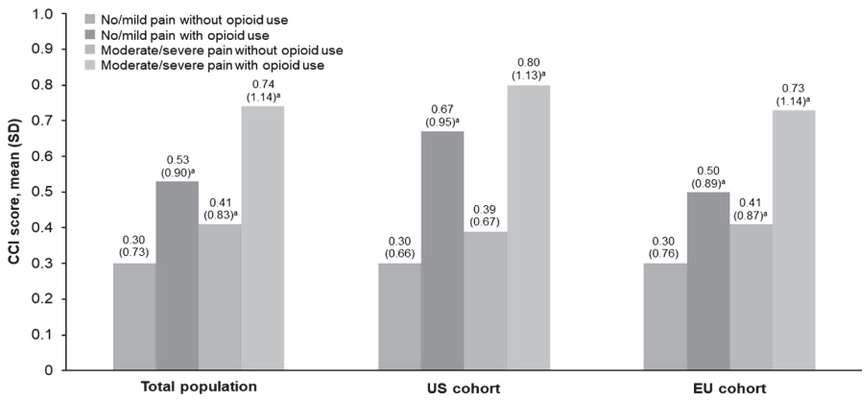

Fig. 2 CCI scores in patients with hip and/or knee OA by pain intensity and opioid use.0.05 versus no/mild pain without opioid use.CCICharlson Comorbidity Index,EU European Union,OA osteoarthritis$SD standard deviation

Key points

- OA is associated with a significant functional burden that can result in disability; not surprisingly, the results from this study demonstrated greater functional impacts with higher pain intensity. Patients with moderate/ severe pain were more likely than patients with no/mild pain to report impairment in physical function and stiffness, specific needs such as for a walking aid or help with daily activities, and that they suffered a fall.

imately two-fold higher with opioid use relative to no opioid use at the same severity level. Moreover, rates of depression or anxiety, osteoporosis, and chronic low back pain were more than twofold higher among patients with moderate/severe pain with current opioid use compared with those with no/mild pain without current opioid use. The majority of patients with moderate/severe pain with or without opioid use reported suffering from a cardiovascular condition or hypertension. Comorbidities are clinically relevant because they may predispose patients to the adverse effects of analgesics (e.g., the gastrointestinal and/or cardiova cular adverse effects of opioids [15] and NSAIDs [32]) and may ultimately affect the choice of pharmacotherapy. These concerns may be most important in patients experiencing greater pain (because they likely have the highest comorbidity burden and require a more intensive analgesic regimen) and in elderly patients (because they may be at higher risk for treatmentrelated toxicity than younger patients).

OA negatively impacts HRQoL [33–38]. Because HRQoL is a multidimensional concept that spans several domains of patient health (i.e., physical functioning, psychologic functioning, social functioning, cognitive functioning, and general well-being), it may be a useful outcome for assessing treatment effects on patients [38]. In this study, HRQoL, as measured by the EQ-5D-5L VAS and utility index, was significantly lower among patients with moderate/ severe pain with or without opioid use compared with those with no/mild pain without opioid use, and the differences in the EQ- 5D-5L utility index scores were clinically relevant, exceeding the estimated MID [26]. HRQoL was also lower among patients who used opioids versus those who did not. The impact on HRQoL observed here may have been related to both symptoms of OA and the untoward effects of treatment. Therefore, therapies that are both effective at controlling OA-related pain and have a low risk-benefit ratio may likely have the most benefit for HRQoL [38].

Previous studies have demonstrated an association between OA and reduced work productivity and daily activity [37, 39–41], and such impairments were also reported by patients in this study. These impairments, which were measured using the WPAI:SHP, were associated with higher pain level and the use of opioids. Work productivity and daily activity impairments were more than twofold higher in patients with moderate/ severe pain with opioid use than in those with no/mild pain without opioid use. Impairment while working due to problem (i.e., presenteeism) was more prevalent than work time missed due to problem (i.e., absenteeism) and was thus the main driver of work impairment in this study. This finding is consistent with the results of other studies in OA showing that presenteeism exerted more of an impact on work productivity than absenteeism [37, 39, 41, 42]. In this study, notable differences were observed in work impairment between the US and EU cohorts, especially with regard to greater absenteeism in the EU, possibly reflect-

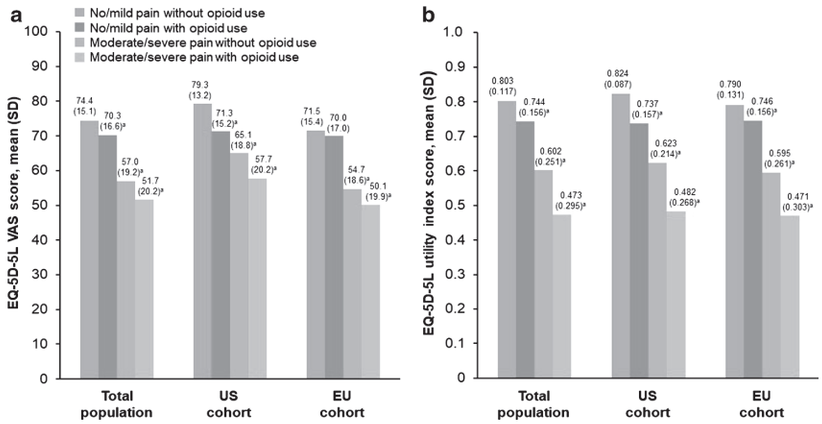

Fig. 3 EQ-5D-5L scores in patients with hip and/or knee OA by pain intensity and opioid use. a VAS scores. b Utility index scores. Higher scores indicate better quality of life. [a]p\ 0.05 versus no/mild pain without opioid use. EQ-5D-5L 5-dimension 5-level EuroQol, EU European Union, OA osteoarthritis, SD standard deviation, VAS visual analog scale

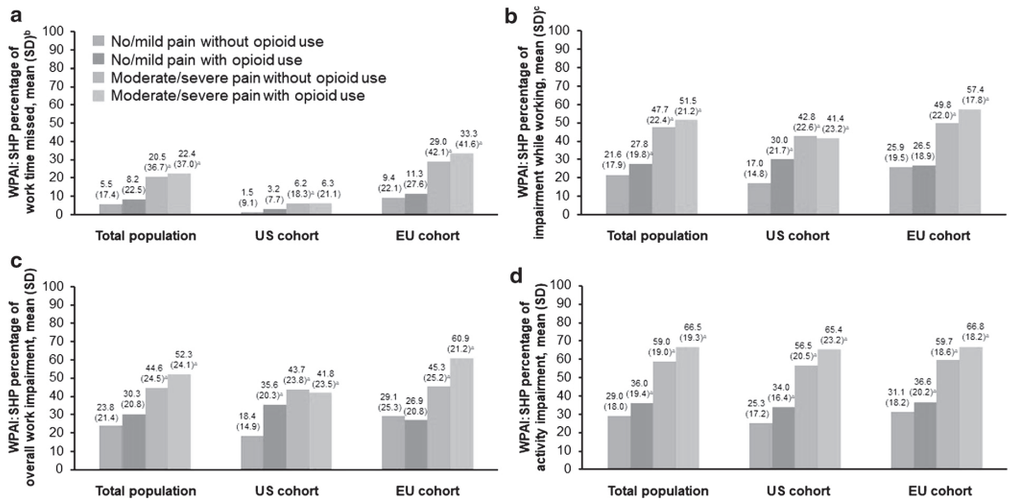

Fig. 4 WPAI:SHP scores in patients with hip and/or knee OA by pain intensity and opioid use. Percentage of work time missed b Percentage of impairment while working. c Percentage of overall work impairment d Percentage of activity impairment. Activity impairment was assessed among all patients; work productivity was assessed among employed patients only. p\ 0.05 versus no/mild pain without opioid use. [b]Absenteeism. [c]Presenteeism. EU European Union, OA osteoarthritis, SD standard deviation, WPAI:SHP Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

Key points

- Rates of depression or anxiety, osteoporosis, and chronic low back pain were more than two-fold higher among patients with moderate/severe pain with current opioid use compared with those with no/mild pain without current opioid use. The majority of patients with moderate/severe pain with or without opioid use reported suffering from a cardiovascular condition or hypertension.
- Comorbidities are clinically relevant because they may predispose patients to the adverse effects of analgesics (e.g., the gastrointestinal and/or cardiovascular adverse effects of opioids and NSAIDs and may ultimately affect the choice of pharmacotherapy.

ing cultural differences in the approach to health and disability in the workplace. Overall, these results underscore the pervasive impact of OA pain on patients' lives, with disease-related burdens placing limitations on recreational, social, and work activities.

This study also demonstrated discrepancies in opioid use for OA pain between the US and the five EU countries combined as well as between the individual EU countries. Opioids were used less frequently in the US than in the EU countries (23% versus 33% of patients). Among the EU countries, opioids were used most frequently in Spain (46%), followed by the UK (40%), Italy (30%), Germany (27%), and France (25%). Although it is not clear what factors contributed to these differences, they may have been related to regional variability in treatment practices, regulations for opioid prescriptions, and patient populations.

The major strength of this study is that paticipating patients reflected the consulting OA population from real-world clinical practice; however, there are limitations that should be considered. This study may have been affected by selection bias given that patients who consulted with their physician more frequently had a greater likelihood of being included in the DSP and information on patients not participating in the survey was not available. There is also an inherent limitation of unmeasured confounding by baseline demographic or disease characteristics because this is a real-world study, and no adjustments were made for potentia confounders. In addition, given the cross-sectional nature of the study, relationships should be considered associative rather thacausal. Furthermore, pairwise comparisons were not conducted between the patient groups, although current opioid use appeared to be associated with a higher burden relative to no opioid use at the same pain level. Recall and social desirability bias may have influenced the results of patient-reported outcomes, although for recall bias, the recall periods were generally short (WPAI had the longest recall at 7 days). Other limitations are the lack of information related to non-opioid analgesic use and equianalgesic opioid dosages (i.e., dosing of two opioids required to produce the same analgesic effect). Despite these potential limitations, these results are strengthened by the large sample size and the variety of outcomes assessed using validated measures (WOMAC, CCI, EQ- 5D-5L, and WPAI:SHP) [22–27].

CONCLUSIONS

In this multinational cross-sectional study, patients with moderate/severe OA pain and those currently using opioids reported significant burdens affecting multiple aspects of their lives. These results indicate that the impact of OA pain is multidimensional, is worsened by increasing pain intensity, and may not be adequately addressed by current treatment strategies.

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Prior Presentation. These data were presented, in part, at the Osteoarthritis Research Society International (OARSI) 2019 World Congress; May 2–5, 2019; Toronto, Onta io, Canada; and the European Congress of Rheumatology (EULAR); June 12–15, 2019; Madrid, Spain.

Disclosures. James Jackson and Jennifer Mellor are employees of Adelphi Real World, which is a paid consultant to Teva Pharmaceutical Industries Ltd. and Regeneron Pharmaceuticals, Inc. Ravi Iyer is an employee of Teva Pharmaceutical Industries Ltd. with stock ownership. Wenhui Wei is an employ-

Key points

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ee of Regeneron Pharmaceuticals, Inc.

Compliance with Ethics Guidelines. The current study used de-identified, aggregated patient data from the Adelphi Disease Sp cific Programme (DSP)TM and was granted exceptions from requiring ethics approval by the Western Institutional Review Board and the Freiburger Ethik Kommission International for the US and EU analysis, respectively.

Data Availability. The datasets generated and/or analyzed during the current study are not publicly available and are considered itellectual property of Adelphi Real World.

■ References

1 O'Neill TW, McCabe PS, McBeth J. Update on the epidemiology, risk factors and disease outcomes of osteoarthritis. Best Pract Res Clin Rheumatol. 2018;32(3):312–26.

2 Osteoarthritis Foundation International (OAFI). Osteoarthritis. 2019. https://oafifoundation.com/ en/what-is-osteoarthritis/. Accessed 6 Dec 2019.

3 Centers for Disease Control and Prevention. Osteoarthritis (OA). 10 Jan 2019. https://www.cdc. gov/arthritis/basics/osteoarthritis.htm. Accessed 6 Dec 2019.

4 Neogi T. The epidemiology and impact of pain in osteoarthritis.Osteoarthrtartil. 2013;21(9):1145–53.

5 Hawker GA, Stewart L, French MR, et al. Understanding the pain experience in hip and knee osteoarthritis–an OARSI/OMERACT initiative. Osteoarthr Cartil. 2008;16(4):415–22.

6 Xie F, Kovic B, Jin X, He X, Wang M, Silvestre C. Economic and humaistic burden of osteoarthritis: a systematic review of large sample studies. Pharmacoeconomics. 2016;34(11):1087–100.

7 Schmidt TW. Approach to osteoarthritis management for the primary care provider. Prim Care. 2018;45(2):361–78.

8 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 Committeefor International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003;62(12):1145–55.

9 Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2005;64(5):669–81.

10 DeMik DE, Bedard NA, Dowdle SB, Burnett RA, McHugh MA, Callaghan JJ. Are we still prescribing opioids for osteoarthritis? J Arthroplasty. 2017;32(12):3578–82.e1.

11 da Costa BR, Nu¨esch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev. 2014;9:CD003115.

12 Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: systematic analytic review. Osteoarthr Cartil. 2016;24(6):962–72.

13 Krebs EE, Gravely A, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. JAMA. 2018;319(9):872–82.

14 Welsch P, Petzke F, Klose P, Ha¨user W. Opioids for chronic osteoarthritis pain: an updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks double-blind duration. Eur J Pain. 2020;24(4):685–703.

15 Ivers N, Dhalla IA, Allan GM. Opioids for osteoarthritis pain: benefits and risks. Can Fam Phys. 2012;58(12):e708.

16 Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 2015;156(4):569–76.

17 Deveza LA, Hunter DJ, Van Spil WE. Too much opioid, too much harm. Osteoarthr Cartil. 2018;26(3):293–5.

18 Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthr Cartil. 2019;27(11):1578–89. https:// doi.org/10.1016/j.joca.2019.06.011.

19 Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2020;72(2):149–62.

20 Anderson P, Benford M, Harris N, Karavali M, Piercy J. Real-world physician and patient behaviour across countries: disease-specif ic programmes—a means to understand. Curr Med Res Opin. 2008;24(11):3063–72.

21 Eurostat. https://ec.europa.eu/eurostat/home. Accessed 1 Apr 2020.

22 Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15(12):1833–40.

23 Bellamy N. WOMAC 3.1 Osteoarthritis Index User Guide XI. July 2016. https://www.womac.com/ womac/index.htm. Accessed 6 Dec 2019.

24 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.

25 EuroQol Group. EQ-5D-5L. 2019. https://euroqol. org/eq-5d-instruments/eq-5d-5l-about/. Accessed 6 Dec 2019.

26 McClure NS, Sayah FA, Xie F, Luo N, Johnson JA. Instrument-defined estimates of the minimally important difference for EQ-5D-5L index scores. Value Health. 2017;20(4):644–50.

27 Reilly MC. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP). August 2010. https://www.reillyassociates.net/WPAI_SHP.html. Accessed 6 Dec 2019.

28 Ayers DC, Franklin PD, Ploutz-Snyder R, Boisvert CB. Total knee replacement outcome and coexisting physical and emotional illness. Clin Or

thop Relat Res. 2005;440:157–61.
29 Caporali R, Cimmino MA, Sarzi-Puttini P, et al. Comorbid conditions in the AMICA study patients: effects on the quality of life and drug pre scriptions by general practitioners and specialists. Semin Arthritis Rheum. 2005;35(1 Suppl 1):31–7.
30 Kadam UT, Jordan K, Croft PR. Clinical comorbidity in patients with os teoarthritis: a case-control study of general practice consulters in En gland and Wales. Ann Rheum Dis. 2004;63(4):408–14.
31 van Dijk GM, Veenhof C, Schellevis F, et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. BMC Musculoskelet Disord. 2008;9:95.
32 Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal an tiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. J Pharm Pharm Sci. 2013;16(5):821–47.
33 Dominick KL, Ahern FM, Gold CH, Heller DA. Health-related quality of life and health service use among older adults with osteoarthritis. Arthri tis Rheum. 2004;51(3):326–31.
34 Picavet HS, Hoeymans N. Health related quality of life in multiple muscu loskeletal diseases: SF-36 and EQ-5D in the DMC3 study. Ann Rheum Dis. 2004;63(6):723–9.
35 Kawano MM, Arau´ jo IL, Castro MC, Matos MA. Assessment of quality of life in patients with knee osteoarthritis. Acta Ortop Bras. 2015;23(6):307–10.
36 Hoogeboom TJ, den Broeder AA, de Bie RA, van den Ende CH. Longitu dinal impact of joint pain comorbidity on quality of life and activity levels in knee osteoarthritis: data from the Osteoarthritis Initiative. Rheumatol ogy (Oxford). 2013;52(3): 543–6.
37 Nakata K, Tsuji T, Vietri J, Jaffe DH. Work impairment, osteoarthritis, and health-related quality of life among employees in Japan. Health Qual Life Outcomes. 2018;16(1):64.
38 Farr Ii J, Miller LE, Block JE. Quality of life in patients with knee osteoar thritis: a commentary on nonsurgical and surgical treatments. Open Or thop J. 2013;7:619–23.
39 Dibonaventura Md, Gupta S, McDonald M, Sadosky A. Evaluating the health and economic impact of osteoarthritis pain in the workforce: re sults from the National Health and Wellness Survey. BMC Musculoskelet Disord. 2011;12:83.
40 Hubertsson J, Petersson IF, Thorstensson CA, Englund M. Risk of sick leave and disability pension in working-age women and men with knee osteoarthritis. Ann Rheum Dis. 2013;72(3):401–5.
41 Kingsbury SR, Gross HJ, Isherwood G, Conaghan PG. Osteoarthritis in Europe: impact on health status, work productivity and use of pharma cotherapies in five European countries. Rheumatology (Ox ford). 2014;53(5):937–47.
42 Dibonaventura Md, Gupta S, McDonald M, Sadosky A, Pettitt D, Silver man S. Impact of self-rated osteoarthritis severity in an employed popu lation: cross-sectional analysis of data from the national health and well ness survey. Health Qual Life Outcomes. 2012;10:30.

■ Ali Mobasheri, Mark Batt

An update on the pathophysiology of osteoarthritis

ABSTRACT :

Introduction: : Osteoarthritis (OA) is one of the most common forms of arthritis. There is accumulating evidence to suggest that OA is an inflammatory disease of the entire synovial joint and has multiple phenotypes. This presents the OA research community with new challenges and opportunities. The main challenge is to understand the root cause of the disease and identify differences and similarities between OA phenotypes. The key opportunity is the possibility of developing personalized and individualized prevention and treatment strategies for OA patients with different phenotypes of the disease. Indeed, it has been suggested that this is the era of 'personalized prevention' for OA. The aim of this mini-review paper is to focus on the pathophysiological aspects of OA development and progression, review the current concepts and discuss the future of personalized medicine for OA.

Methods: The PubMed/MEDLINE bibliographic database was searched using the keywords 'pathophysiology' and 'osteoarthritis'.

Results: The PubMed/MEDLINE search yielded more than 12,000 relevant papers. A selection of these papers is reviewed here.

Conclusions: : There has been slow but steady progress in our understanding of the pathophysiology of OA over the last two decades. However, large gaps remain in our knowledge of OA pathogenesis and this impacts negatively on patients and drug development pipeline. In the absence of new pharmaceutical agents and disease modifying osteoarthritis drugs (DMOADs) it is clear that lifestyle modification and physical activity are important and may delay the need for surgical intervention.

1. INTRODUCTION

Osteoarthritis (OA), also known as osteoarthrosis or degenerative joint disease, is a disease of synovial joints [1]. It is characterized by progressive deterioration and loss of articular cartilage with concomitant structural and functional changes in the entire joint, including the synovium, meniscus (in the knee), periarticular ligaments, and subchondral bone [2]. OA is actually one of the most common, costly and disabling forms of joint disease, being far more common than rheumatoid arthritis (RA) and other forms of joint disease [3]. Cohort studies have demonstrated that after age, obesity and metabolic disease are major risk factors for the development of OA [4,5]. OA is now generally accepted to be an inflammatory and biomechanical whole-organ disease that is influenced by a number of factors including joint shape and dysplasia [6], obesity [7], synovitis [8– 10], complement proteins [11], systemic inflammatory mediators [1,12], inflammaging [13,14], innate immunity [15], the low-grade inflammation [16] induced by metabolic syndrome [1,17] and diabetes mellitus [18]. However, despite the fact that all joint tissues are implicated in disease initiation and progression in OA, it is the articular cartilage component that has received the most attention in the context of aging, injury and disease [2]. Articular cartilage is a flexible and mechanically compliant connective tissue found at the end of long bones in articulating joints and in the intervertebral disc [2]. Its main function is to provide a smooth, lubricated surface for articulation and to facilitate the transmission of loads with a low frictional coefficient [19]. Throughout life, cartilage is continually remodeled as chondrocytes replace the degraded matrix macromolecules with newly synthesized components, although it is recognized that this is an exceptionally slow process in adults; proteoglycan turnover can take up to 2 decades whereas the half-life of collagen is estimated to range from several decades to more than 100 years [20–22]. Although articular cartilage can tolerate a tremendous amount of intensive and repetitive physical stress, it manifests a striking inability to heal even a minor injury [2]. This makes joints particularly sensitive to degenerative processes and the development of OA. The root cause of OA is not completely understood. However, the biomechanical forces that place inappropriate levels of stress on the joints (e.g., excessive or abnormal load bearing, postural or orthopedic abnormalities, or traumatic injuries) that destabilize the joint are thought to interact with other environmental, systemic (i.e. biochemical, metabolic) and genetic factors to contribute to the pathogenesis of OA. The disease has traditionally been defined as a prototypical non-inflammatory arthropathy, but today there is compelling evidence to suggest that in addition to being a disease of biomechanics [23], it has inflammatory and metabolic components [1,16,24–27].

The aim of this concise review article is to provide an update on the pathophysiology of OA. We focus on the pathophysiology and pathogenesis of OA, review some of the current concepts in OA research and discuss the future of personalized medicine for OA. In the absence of disease modifying OA drugs (DMOADs) personalized therapy should include lifestyle evaluation, physical therapy and rehabilitation. Even if structure modifying drugs for OA are on the horizon, it will take decades before we have epidemiological data on efficacy. Therefore, as we eagerly anticipate the development of novel DMOADs it would be prudent to focus on OA prevention rather than treatment. We will set the scene by providing an update on the global burden of OA and the spiraling cost of treatment [3] before discussing the pathophysiology of OA and the need for identifying early inflammatory events and targeting these alterations [12] to ameliorate the major symptoms such as inflammation and pain in OA patients [24].

Key points

- Osteoarthritis (OA), also known as osteoarthrosis or degenerative joint disease, is a disease of synovial joints. It is characterized by progressive deterioration and loss of articular cartilage with concomitant structural and functional changes in the entire joint, including the synovium, meniscus (in the knee), periarticular ligaments, and subchondral bone.
- OA is actually one of the most common, costly and disabling forms of joint disease, being far more common than rheumatoid arthritis (RA) and other forms of joint disease.
- OA is now generally accepted to be an inflammatory and biomechanical whole-organ disease that is influenced by a number of factors including:
- Joint Shape and Dysplasia
- Obesity
- Synovitis
- Complement Proteins
- Systemic Inflammatory Mediators
- Inflammaging
- Innate Immunity
- The Low-Grade Inflammation
- Induced By Metabolic Syndrome
- Diabetes Mellitus

2. The global burden of OA

OA is the leading cause of chronic disability globally in individuals older than 70 years and has been designated a 'priority disease' by the World Health Organization (WHO) (report WHO/ EDM/PAR/2004.71). OA is one of the ten most disabling diseases in industrialized countries. In the Global Burden of Disease 2010 study, hip and knee OA was ranked as the 11th highest contributor to global disability [3]. The prevalence of OA is set to increase in parallel with the increase in the number of people aged 60 years and older and the rise in obesity across the world. In the United States alone OA is the highest cause of work loss and affects more than 20 million individuals, costing the US economy greater than US$100 billion annually [28,29]. OA represents one of the top 5 healthcare costs in Europe [3]. In the United Kingdom a third of people aged 45 and over (8.75 million people) have sought treatment for OA, and at least half of these individuals have knee OA (half of all people seeking treatment for OA have knee OA). The number of people in the UK with knee OA is estimated to increase to 6.5 million by 2020 (allowing for the increasing size of the aging population and the rising levels of overweight and obesity). In France, the direct and indirect costs of OA have been estimated by Le pen et al., in the "COART" France study [30]. The authors used a top-down approach with nationwide data from 2001 to 2003 and estimated the direct costs of OA at s1.6 billion, representing approximately 1.7% of the budget of the French health insurance system. The authors reported a 156% increase in direct medical costs compared with 1993, which was related to an increase in the number of OA patients (+54%). In Canada 4.5 million (one in six) Canadians aged 15 years and older report having arthritis and by 2031, approximately seven million Canadians (one in five) are expected to have arthritis. In Australia OA is the leading cause of chronic pain, disability and early retirement due to ill health and AU$2 million people live with OA; the annual cost of OA to health system is AU$2 billion AUD in joint replacements for OA with AU$1.3 billion paid for welfare payments annually. There are no up-to-date estimates of the global economic cost of OA although a 1997 analysis of the economic costs of musculoskeletal disorders in the world's 5 industrialized countries (Australia, Canada, France, United Kingdom, and United States), in which OA was the most common of these disorders, found a rising trend of costs that had, by then, reached between 1% and 2.5% ofthe gross national product of these countries [31]. Even if an updated report of global economic burden had been published more recently, it would undoubtedly underestimate the true cost burden to the world's health and social care systems.

3. Modifiable and non-modifiable OA risk factors

Certain factors have been shown to be associated with a greater risk of developing OA. According to the US Centers for Disease Control and Prevention2 and the Mayo Clinic3 some of these risk factors for OA are modifiable whereas others are not. The most important OA risk factors are age, gender, overweight/obesity, joint trauma/sports injuries (and the consequent joint instability and muscle laxity), certain occupations that place repetitive stress on a particular joint, genetics (well beyond the scope of this review), bone deformities, metabolic disease (i.e. diabetes), endocrine disorders and having previously had other rheumatic diseases such as RA and gout. The risk of developing most types of arthritis increases with age and OA is certainly no exception [32]. Gender is another critical risk factor for OA. Indeed most types of arthritis are more common in women and 60% of all people with arthritis are women so perhaps it is not surprising that the female sex also represents a significant risk factor for OA [33]. It has been hypothesized that leptin may be a systemic or local factor that mediates the metabolic link between obesity and OA [33]. Leptin and other adipocytokines (adipokines) may actually be the missing links accounting for the gender disparity toward the disease [34–36].

Some of the above are non-modifiable risk factors for the development of OA. There is clinical evidence to suggest that the risk for developing OA can be mitigated and reduced by weight management, avoiding obesity/overweight, maintaining high levels of mobility and avoiding sedentary lifestyles. The challenge will be managing comorbidities (i.e. diabetes, cardiovascular diseases) and mitigating the risks of joint injury. Some of the above are likely to influence the course of disease progression. Experimental approaches using animal models and clinical

2. The global burden of OA

OA is the leading cause of chronic disability globally in individuals older than 70 years and has been designated a 'priority disease' by the World Health Organization (WHO) (report WHO/ EDM/PAR/2004.71). OA is one of the ten most disabling diseases in industrialized countries. In the Global Burden of Disease 2010 study, hip and knee OA was ranked as the 11th highest contributor to global disability [3]. The prevalence of OA is set to increase in parallel with the increase in the number of people aged 60 years and older and the rise in obesity across the world. In the United States alone OA is the highest cause of work loss and affects more than 20 million individuals, costing the US economy greater than US$100 billion annually [28,29]. OA represents one of the top 5 healthcare costs in Europe [3]. In the United Kingdom a third of people aged 45 and over (8.75 million people) have sought treatment for OA, and at least half of these individuals have knee OA (half of all people seeking treatment for OA have knee OA). The number of people in the UK with knee OA is estimated to increase to 6.5 million by 2020 (allowing for the increasing size of the aging population and the rising levels of overweight and obesity). In France, the direct and indirect costs of OA have been estimated by Le pen et al., in the "COART" France study [30]. The authors used a top-down approach with nationwide data from 2001 to 2003 and estimated the direct costs of OA at [s1].6 billion, representing approximately 1.7% of the budget of the French health insurance system. The authors reported a 156% increase in direct medical costs compared with 1993, which was related to an increase in the number of OA patients (+54%). In Canada 4.5 million (one in six) Canadians aged 15 years and older report having arthritis and by 2031, approximately seven million Canadians (one in five) are expected to have arthritis. In Australia OA is the leading cause of chronic pain, disability and early retirement due to ill health and AU$2 million people live with OA; the annual cost of OA to health system is AU$2 billion AUD in joint replacements for OA with AU$1.3 billion paid for welfare payments annually. There are no up-to-date estimates of the global economic cost of OA although a 1997 analysis of the economic costs of musculoskeletal disorders in the world's 5 industrialized countries (Australia, Canada, France, United Kingdom, and United States), in which OA was the most common of these disorders, found a rising trend of costs that had, by then, reached between 1% and 2.5% ofthe gross national product of these countries [31]. Even if an updated report of global economic burden had been published more recently, it would undoubtedly underestimate the true cost burden to the world's health and social care systems.

3. Modifiable and non-modifiable OA risk factors

Certain factors have been shown to be associated with a greater risk of developing OA. According to the US Centers for Disease Control and Prevention[2] and the Mayo Clinic[3] some of these risk factors for OA are modifiable whereas others are not. The most important OA risk factors are age, gender, overweight/obesity, joint trauma/sports injuries (and the consequent joint instability and muscle laxity), certain occupations that place repetitive stress on a particular joint, genetics (well beyond the scope of this review), bone deformities, metabolic disease (i.e. diabetes), endocrine disorders and having previously had other rheumatic diseases such as RA and gout. The risk of developing most types of arthritis increases with age and OA is certainly no exception [32]. Gender is another critical risk factor for OA. Indeed most types of arthritis are more common in women and 60% of all people with arthritis are women so perhaps it is not surprising that the female sex also represents a significant risk factor for OA [33]. It has been hypothesized that leptin may be a systemic or local factor that mediates the metabolic link between obesity and OA [33]. Leptin and other adipocytokines (adipokines) may actually be the missing links accounting for the gender disparity toward the disease [34–36].

Some of the above are non-modifiable risk factors for the development of OA. There is clinical evidence to suggest that the risk for developing OA can be mitigated and reduced by weight management, avoiding obesity/overweight, maintaining high levels of mobility and avoiding sedentary lifestyles. The challenge will be managing comorbidities (i.e. diabetes, cardiovascular diseases) and mitigating the risks of joint injury. Some of the above are likely to influence the course of disease progression. Experimental approaches using animal models and clinical

Key points

- Articular cartilage is a flexible and mechanically compliant connective tissue found at the end of long bones in articulating joints and in the intervertebral disc. Its main function is to provide a smooth, lubricated surface for articulation and to facilitate the transmission of loads with a low frictional coefficient.
- Throughout life, cartilage is continually remodeled as chondrocytes replace the degraded matrix macromolecules with newly synthesized components, although it is recognized that this is an exceptionally slow process in adults; proteoglycan turnover can take up to 2 decades whereas the half-life of collagen is estimated to range from several decades to more than 100 years.
- Although articular cartilage can tolerate a tremendous amount of intensive and repetitive physical stress, it manifests a striking inability to heal even a minor injury. This makes joints particularly sensitive to degenerative processes and the development of OA. The root cause of OA is not completely understood.

Key points

- The prevalence of OA is set to increase in parallel with the increase in the number of people aged 60 years and older and the rise in obesity across the world. In the United States alone OA is the highest cause of work loss and affects more than 20 million individuals, costing the US economy greater than US$100 billion annually. OA represents one of the top 5 healthcare costs in Europe.
- In the United Kingdom a third of people aged 45 and over (8.75 million people) have sought treatment for OA, and at least half of these individuals have knee OA (half of all people seeking treatment for OA have knee OA). The number of people in the UK with knee OA is estimated to increase to 6.5 million by 2020 (allowing for the increasing size of the aging population and the rising levels of overweight and obesity).

7.Disruption in circadian clocks and rhythms

The circadian rhythm is a 24-hour cycle in the physiological processes of all animals. Circadian rhythm are strictly set, tightly regulated and endogenously generated, although they can be modulated by external cues such as light and dark cycles. The study of circadian clocks and circadian rhythms is starting to make a significant impact on rheumatology, orthopedics and cartilage biology [48]. Studies in murine chondrocytes have shown that the circadian clock regulates genes controlling key aspects of cartilage homeostasis [49]. Indeed the catabolic cytokines implicated in the pathophysiology of OA can disrupt the circadian clock and the expression of clock-controlled genes in cartilage via an NFkBdependent pathway [50]. The chondrocyte core clock gene and transcription factor BMAL1 is one of the key genes that controls cartilage homeostasis and integrity. A new study by Dudek and colleagues shows that BMAL1 is disrupted in human OA cartilage and in aged mouse cartilage. The authors also show that targeted Bmal1 ablation in murine chondrocytes abolishes their circadian rhythm and causes progressive degeneration of articular cartilage. The BMAL1 gene directs the circadian expression of many genes implicated in cartilage homeostasis, including those involved in chondrocyte apoptosis, catabolic and anabolic pathways. Ablation of this gene decreases expression of the major extracellular matrixrelated genes Sox9, Acan, and Col2a1. This is the first study that links BMAL1 to the maintenance and repair of articular cartilage. This paper suggests that circadian rhythm disruption is a risk factor for the pathogenesis and progression of degenerative joint diseases such as OA. Clock genes are also believed to regulate reactive oxygen species (ROS) homeostasis and oxidative stress responses suggesting that disruption of circadian rhythms may exacerbate inflammaging and enhance ROS levels and oxidative stress signaling in OA [51].

8. Sleep disturbance and depression in OA

The relationship between OA and sleep might seem obvious if we focus on pain, which clearly is an important part of the equation, but recent research suggests that the connection goes beyond pain and OA symptoms. Indeed,the relationship is far more complex and could indeed be reciprocal. Rather than OA causing insomnia, the two conditions are thought to coexist and may be mechanistically linked. Parmelee et al. have proposed that sleep disturbance

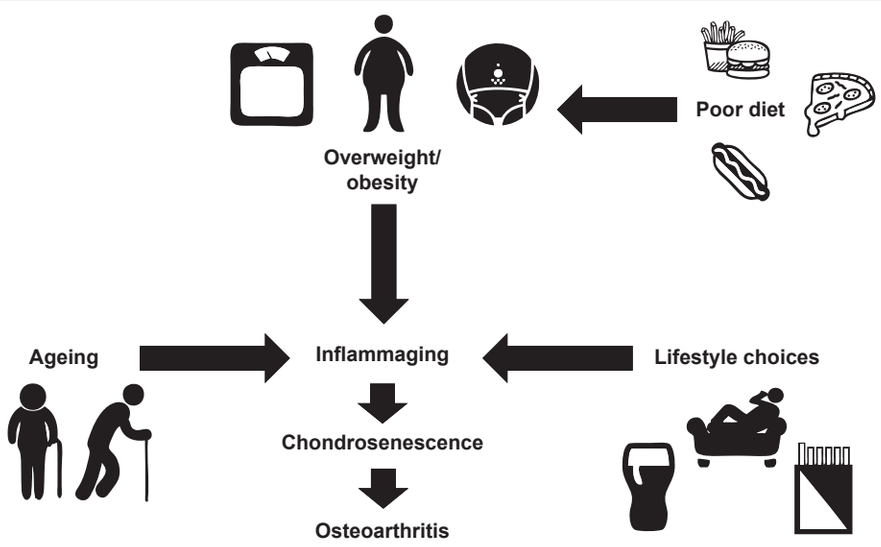

Fig. 1. The convergence of aging, obesity and lifestyle choices in the development of inflammaging and chondrosenescence in OA.

Fig. 2. Moderate intensity exercises that are recommended for OA patients.

in OA is linked with pain, disability, and depressive symptoms [52]. Their work highlights the link between sleep disturbance, pain and disability in OA. Although this is a new and under-researched area, papers are gradually emerging to support the notion that lack of sleep and disease progression are closely linked in humans and animals [53]. The study by Parmelee and colleagues has identified a new and important point of intervention that may provide a new preventive strategy for OA-related functional decline among patients whose sleep is disrupted by OArelated pain[52]. Aside from sleep disturbance another potentially important factor in OA progression is depression. Depression appears to play a strong role in the sleep-pain linkage, particularly when pain is particularly severe. The unique predictive role of sleep in the progression of disability requires further study but may be an important point of i tervention to prevent OA-related functional decline among persons whose sleep is disrupted by OArelated pain. It will be very interesting to establish whether drugs that can improve the quality of sleep might slow disease progression in cohorts of OA patients. Future work in this area should provide further insight into the inte play between circadian rhythms and cartilage homeostasis and may reveal new therapeutic targets for the treatment of OA. On a more practical level, OA patients may wish to explore ways to improve their sleep without using sleep aids and sleep medicines that can have undesired side effects. However, hormones such as melatonin are being used as a pharmacologic aid to sleep, especially in sleep disorders affecting circadian rhythms. Interestingly, melatonin has anti-oxidant properties and is thought to modulate the pathogenesis of inflammatory autoimmune diseases. However, we know nothing about the effects of melatonin on articular cartilage and chondrocytes. These suggestions and sleep strategies may seem trivial but they represent good common sense:

- not eating a heavy meal before bed–eating a heavy meal before bedtime can disrupt sleep rhythms;
- not drinking heavily caffeinated beverages or large quantities of alcohol before bed;
- not watching television and tablets in the bedroom before sleeping;
- keeping the bedroom comfortably cool (65–68 8F, 18–20 8C), quiet and dark (avoiding external light pollution).

9. Exercise and physical activity in the prevention and management of OA

According to reports published by the WHO,4 we live in a world where the population is becoming increasingly overweight,

Key points

- The risk of developing most types of arthritis increases with age and OA is certainly no exception. Gender is another critical risk factor for OA. Indeed most types of arthritis are more common in women and 60% of all people with arthritis are women so perhaps it is not surprising that the female sex also represents a significant risk factor for OA.
- It has been hypothesized that leptin may be a systemic or local factor that mediates the metabolic link between obesity and OA. Leptin and other adipocytokines (adipokines) may actually be the missing links accounting for the gender disparity toward the disease.

Key points

- The relationship between OA and sleep might seem obvious if we focus on pain, which clearly is an important part of the equation, but recent research suggests that the connection goes beyond pain and OA symptoms. Indeed, the relationship is far more complex and could indeed be reciprocal. Rather than OA causing insomnia, the two conditions are thought to coexist and may be mechanistically linked.

obese and sedentary. This toxic combination is contributing to an increasing burden of long-term conditions that for most health services in the world is financially unsustainable. Whilst obesity is a well-known risk factor for many chronic diseases through the metabolic syndrome a lack of physical activity is also an independent risk factor, as is the number of hours spent sitting or lying (sedentariness) [54]. Consequently, healthcare systems around the world are developing strategies trying to encourage health and wellness through increased levels of daily physical activity. Physical activity, exercise and sport form a continuum of human exertion. The precise definitions are less important for a public health message, which should encourage more people to be more active more of the time. Nonetheless it is appreciated that some of these activities can potentially result in joint damage, injury and OA. In this section we summarize the existing data and current opinion.

Physical activity is essential for optimal health. It is acknowledged that increasing physical activity and reducing sedentary hours would go a long way to preserving health (physical and mental) and preventing increasing burden of long-term conditions. Moreover, it is recognized that physical activity may be used as treatment for several chronic diseases whose etiology includes poor lifestyle choices. Globally there is an understanding that physical activity and exercise are beneficial with much data to support its prescription, however, the exact prescription program is yet to be found. This is fundamental as most healthcare systems around the world have shrinking resources and thus it is important to define a commissionable product with known effectiveness. There is increasing appreciation of a dichotomy in the effects of exercise and sport on the health of the musculoskeletal system and particularly joints. Non-elite or recreational activities typically confer health benefits. A number of moderate intensity exercises are actually recommended for OA patients (Fig. 2).

Conversely, participation in elite level activities, particularly contact or collision sports, which are associated with injury, are more associated with post-traumatic OA [55,56]. There is increasingly good evidence that recreational running, as an example of a non-contact/collision activity, is not associated with an increased prevalence or progression of knee OA [57,58]. These studies suggest that long-distance running among healthy older individuals is not associated with accelerated radiographic OA. In fact, long-distance running might even have a

Fig. 3. Vigorous intensity exercises that are not suitable for patients with established OA.

protective effect against joint degeneration. However, a number of vigorous intensity exercises may not be suitable for patients with established OA (Fig. 3).

Another important issue that is worthy of discussion is the effect of acute injury on lower limbs and the risk of OA development. The order of prevalence of lower limb OA is typically knee, hip and lastly foot and ankle. However, the association with OA in these joints is almost reverse when one considers injury as a key etiological factor – it is the ankle that ranks first with nearly 80% of ankle OA being post-traumatic in origin. However, unlike the knee there is a significant latency between injury and onset of symptomatic ankle OA [59,60]. Thus for ce tain joints injury is the primary risk factor for the subsequent development of OA, although the mechanisms have yet to be fully elucidated. It is also appreciated that injury within a given 'node' of the kinetic chain can predispose to injury elsewhere – so that an incompletely rehabilitated ankle sprain may act as a precursor to a subsequent knee injury.

Reviewing the risks and benefits of physical activity and overall musculoskeletal health and OA is beyond the scope of a commissioned article entitled:"Pathophysiology of Osteoarthritis". However, there is an increasing body of evidence to suggest that physical activity is essential for cardiovascular, metabolic,musculoskeletal and mental health. A recent systematic review of exercise for knee OA extracted data from 54 studies to provide high-quality evidence to indicate that land-based therapeutic exercise provides benefits for patients [61]. The study reports that short-term benefits were sustained for at least two to six months after cessation of formal treatment in terms of reduced knee pain. There was moderate-quality evidence shows improvement in physical function among people with knee OA. Interestingly, since the participants in the trials that were included in this systematic review were aware of the nature of their treatment, this may have contributed to their improvement. Another recent systematic review has evaluated the effects of aquatic exercise for people with knee or hip OA. The study provides moderate quality evidence that aquatic exercise may have small, short-term, and clinically relevant effects on patient-reported pain, disability, and quality of life in people with knee and hip OA [62]. Promoting and encouraging physical activity in older adults at risk for developing OA is important and has been shown to be associated with maintained physical function mediated by muscle strength [63]. Positive effects have been reported across a wide range of physical activities, including one of the simplest forms of exercise: walking. A positive effect has also been associated with more daily walking plus intensive diet and exercise among adults with painful knee OA [64,65]. This positive effect may be an important psychological factor to consider for promoting physical activity among people with painful knee OA.

10. Conclusions

It has been over a decade since Wim van den Berg and Johanne Martel-Pelletier published short papers on the "Pathophysiology of osteoarthritis" [66,67]. Knowledge of the pathophysiology of OA is rapidly expanding. Recently published reviews on OA suggest that the disorder is complex and multifactorial, with numerous genetic, biological, and biomechanical components [68]. OA is now viewedas an inflammatory disease with multiple phenotypes [32]. This presents the OA research community with new challenges and opportunities. The key challenge is identifying the differences and similarities between the phenotypes. The main opportunity is the possibility of developing personalized and individualized prevention and treatment strategies for OA patients with different forms of the disease [69,70]. Chronic, low-grade inflammation in OA is now known to contribute to symptoms and disease progression and multiple mediators are emerging as regulators of this process [12]. However, in the absence of new pharmaceutical agents and disease modifying osteoarthritis drugs (DMOADs) it is clear that lifestyle modification and physical activity are important and may delay the need for surgical intervention. This concept should be especially relevant to the Annals of Physical and Rehabilitation Medicine and the readers of this Special Issue on "Osteoarthritis".

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Key points

- the effects of melatonin on articular cartilage and chondrocytes. These suggestions and sleep strategies may seem trivial but they represent good common sense:
- Not eating a heavy meal before bed–eating a heavy meal before bedtime can disrupt sleep rhythms
- Not drinking heavily caffeinated beverages or large quantities of alcohol before bed
- Not watching television and tablets in the bedroom before sleeping
- Keeping the bedroom comfortably cool (65–68 8f, 18–20 8c), quiet and dark (avoiding external light pollution)

Key points

- According to reports published by the WHO,4 we live in a world where the population is becoming increasingly overweight, obese and sedentary. This toxic combination is contributing to an increasing burden of long-term conditions that for most health services in the world is financially unsustainable.
- Whilst obesity is a well-known risk factor for many chronic diseases through the metabolic syndrome a lack of physical activity is also an independent risk factor, as is the number of hours spent sitting or lying (sedentariness).

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Disclosure of interest

The authors declare that they have no competing interest.

References

1 Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthr Cartil 2013;21:16–21.
2 Buckwalter JA, Mankin HJ. Articular cartilage: degeneration and osteo arthritis, repair, regeneration, and transplantation. Instr Course Lect 1998;47:487–504.
3 Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73:1323–30.
4 Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. Ann Intern Med 1988;109:18–24.
5 Aspden RM, Scheven BA, Hutchison JD. Osteoarthritis as a systemic order including stromal cell differentiation and lipid metabolism. Lancet 2001;357: 1118–20.
6 Baker-LePain JC, Lane NE. Relationship between joint shape and the development of osteoarthritis. Curr Opin Rheumatol 2010;22:538–43.
7 Bliddal H, Leeds AR, Christensen R. Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons – a scoping review. Obes Rev 2014;15: 578–86.
8 De Lange-Brokaar BJ, Ioan-Facsinay A, van Osch GJ, Zuurmond AM, Schoones J, Toes RE, et al. Synovial inflammation, immune cells and their cytokines in osteoarthritis: a review. Osteoarthr Cartil 2012;20:1484–99.
9 Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis patho genesis. Bone 2012;51:249–57.
10 Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol 2010;6:625–35.
11 Wang Q, Rozelle AL, Lepus CM, Scanzello CR, Song JJ, Larsen DM, et al. Identification of a central role for complement in osteoarthritis. Nat Med 2011;17:1674–9.
12 Liu-Bryan R, Terkeltaub R. Emerging regulators of the inflammatory pro cess in osteoarthritis. Nat Rev Rheumatol 2015;11:35–44.
13 Mobasheri A, Matta C, Za´ka´ny R, Musumeci G. Chondrosenescence: definition, hallmarks and potential role in the pathogenesis of osteoar thritis. Maturitas 2015;80:237–44.
14 Greene MA, Loeser RF. Aging-related inflammation in osteoarthritis. Osteoarthr Cartil 2015;23:1966–71.
15 Orlowsky EW, Kraus VB. The role of innate immunity in osteoarthritis: when our first line of defense goes on the offensive. J Rheumatol 2015;42:363–71.
16 Sellam J, Berenbaum F. Is osteoarthritis a metabolic disease? Joint Bone Spine 2013;80:568–73.
17 Courties A, Gualillo O, Berenbaum F, Sellam J. Metabolic stress-induced joint inflammation and osteoarthritis. Osteoarthr Cartil 2015;23:1955–65.
18 Louati K, Vidal C, Berenbaum F, Sellam J. Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analy sis. RMD Open 2015;1:e000077.
19 Sophia Fox AJ, Bedi A, Rodeo SA. The basic science of articular cartilage: structure, composition, and function. Sports Health 2009;1:461–8.
20 Otero M, Favero M, Dragomir C, Hachem KE, Hashimoto K, Plumb Deal. Human chondrocyte cultures as models of cartilage-specific gene regu lation. Methods Mol Biol 2012;806:301–36.
21 Eyre DR, Weis MA, Wu JJ. Articular cartilage collagen: an irreplaceable framework? Eur Cell Mater 2006;12:57–63.
22 Masuda K, Sah RL, Hejna MJ, Thonar EJ. A novel two-step method for the formation of tissue-engineered cartilage by mature bovine chondro cytes: the alginate-recovered-chondrocyte (ARC) method. J Orthop Res 2003;21:139–48.
23 Felson DT. Osteoarthritis as a disease of mechanics. Osteoarthr Cartil 2013; 21:10–5.
24 Rahmati M, Mobasheri A, Mozafari M. Inflammatory mediators in os teoarthritis: a critical review of the state-of-the-art, current prospects, and future challenges. Bone 2016;85:81–90.
25 Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoar thritis. Nat Rev Rheumatol 2012;8:729–37.
26 Wang X, Hunter D, Xu J, Ding C. Metabolic triggered inflammation in osteoarthritis. Osteoarthr Cartil 2015;23:22–30.
27 Malemud CJ. Biologic basis of osteoarthritis: state of the evidence. Curr Opin Rheumatol 2015;27:289–94.
28 Sandell LJ. Etiology of osteoarthritis: genetics and synovial joint develop ment. Nat Rev Rheumatol 2012;8:77–89.
29 Centers for Disease Control and Prevention (CDC). Prevalence of doc tor-diagnosed arthritis and arthritis-attributable activity limitation—United States,2010–2012. MMWR Morb Mortal Wkly Rep 2013;62:869–73.
30 Le Pen C, Reygrobellet C, Ge´ rentes I. Financial cost of osteoarthritis in France. The "COART" France study. Joint Bone Spine 2005;72:567–70.
31 March LM, Bachmeier CJ. Economics of osteoarthritis: a global perspec tive. Baillieres Clin Rheumatol 1997;11:817–34.
32 Conaghan PG. Osteoarthritis in 2012: parallel evolution of OA pheno types and therapies. Nat Rev Rheumatol 2013;9:68–70.
33 Teichtahl AJ, Wluka AE, Proietto J, Cicuttini FM. Obesity and the female sex, risk factors for knee osteoarthritis that may be attribut

able to systemic or local leptin biosynthesis and its cellular effects. Med Hypoth eses 2005;65:312–5.
34 Terlain B, Dumond H, Presle N, Mainard D, Bianchi A, Loeuille D, et al. [Is leptin the missing link between osteoarthritis and obesi ty?] Ann Pharm Fr 2005; 63:186–93.
35 Scotece M, Mobasheri A. Leptin in osteoarthritis: focus on articular car tilage and chondrocytes. Life Sci 2015;140:75–8.
36 Terlain B, Presle N, Pottie P, Mainard D, Netter P. [Leptin: a link between obesity and osteoarthritis?] Bull Acad Natl Med 2006;190:1421–35. dis cussion 1435.
37 Ehrlich GE. Osteoarthritis beginning with inflammation. Definitions and correlations. JAMA 1975;232:157–9.
38 Ehrlich GE. Osteoarthritis beginning with inflammation. Definitions and correlations. 1975. Bull World Health Organ 2003;81:691–3.
39 Haugen IK, Mathiessen A, Slatkowsky-Christensen B, Magnusson K, Bøyesen P, Sesseng S, et al. Synovitis and radiographic progression in non-erosive and erosive hand osteoarthritis: is erosive hand osteoarthri tis a separate inflammatory phenotype? Osteoarthr Cartil 2016;24:647–54.
40 Haugen IK, Slatkowsky Christensen B, Bøyesen P, Sesseng S, van der Heijde D, Kvien TK. Increasing synovitis and bone marrow lesions are associated with ncident joint tenderness in hand osteoarthritis. Ann Rheum Dis 2015;75:702–8.
41 Lo´ pez-Ota´n C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell 2013;153:1194–217.
42 Loeser RF. Age-related changes in the musculoskeletal system and the development of osteoarthritis. Clin Geriatr Med 2010;26:371–86.
43 Goldring MB. Chondrogenesis, chondrocyte differentiation, and articu lar cartilage metabolism in health and osteoarthritis. Ther Adv Musculo skelet Dis 2012;4:269–85.
44 Van der Kraan PM, van den Berg WB. Chondrocyte hypertrophy and osteoarthritis: role in initiation and progression of cartilage degenera tion? Osteoarthr Cartil 2012;20:223–32.
45 Fernandes JC, Martel-Pelletier J, Pelletier JP. The role of cytokines in osteoarthritis pathophysiology. Biorheology 2002;39:237–46.
46 Martin JA, Buckwalter JA. Aging, articular cartilage chondrocyte senes cence and osteoarthritis. Biogerontology 2002;3:257–64.
47 Carame´ s B, Olmer M, Kiosses WB, Lotz MK. The relationship of auto phagy defects to cartilage damage during joint aging in a mouse model. Arthritis Rheumatol 2015;67:1568–76.
48 Gossan N, Boot-Handford R, Meng QJ. Ageing and osteoarthritis: a cir cadian rhythm connection. Biogerontology 2015;16:209–19.
49 Gossan N, Zeef L, Hensman J, Hughes A, Bateman JF, Rowley L, et al. The circadian clock in murine chondrocytes regulates genes controlling key aspects of cartilage homeostasis. Arthritis Rheum 2013;65:2334–45.
50 Guo B, Yang N, Borysiewicz E, Dudek M, Williams JL, Li J, et al. Catabolic cytokines disrupt the circadian clock and the expression of clock-cont rolled genes in cartilage via an NFkB-dependent pathway. Osteoarthr Cartil 2015; 23:1981–8.
51 Lepetsos P, Papavassiliou AG. ROS/oxidative stress signaling in osteoar thritis. Biochim Biophys Acta 2016;1862:576–91.
52 Parmelee PA, Tighe CA, Dautovich ND. Sleep disturbance in osteoarthri tis: linkages with pain, disability, and depressive symptoms. Arthritis Care Res (Hoboken) 2015;67:358–65.
53 Knazovicky D, Tomas A, Motsinger-Reif A, Lascelles BD. Initial evalua tion of nighttime restlessness in a naturally occurring canine model of osteoarthritis pain. PeerJ 2015;3:e772.
54 Owen N, Salmon J, Koohsari MJ, Turrell G, Giles-Corti B. Sedentary be haviour and health: mapping environmental and social contexts to un derpin chronic disease prevention. Br J Sports Med 2014;48:174–7.
55 Bennell K, Hunter DJ, Vicenzino B. Long-term effects of sport: prevent ing and managing OA in the athlete. Nat Rev Rheumatol 2012;8:747–52.
56 Martin JA, Brown T, Heiner A, Buckwalter JA. Post-traumatic osteoar thritis: the role of accelerated chondrocyte senescence. Biorheology 2004;41: 479–91.
57 Chakravarty EF, Hubert HB, Lingala VB, Zatarain E, Fries JF. Long dis tance running and knee osteoarthritis. A prospective study. Am J Prev Med 2008; 35:133–8.
58 Cymet TC, Sinkov V. Does long-distance running cause osteoarthritis? J Am Osteopath Assoc 2006;106:342–5.
59 Valderrabano V, Horisberger M, Russell I, Dougall H, Hintermann B. Eti ology of ankle osteoarthritis. Clin Orthop Relat Res 2009;467:1800–6.
60 Friel NA, Chu CR. The role of ACL injury in the development of posttrau maticknee osteoarthritis. Clin Sports Med 2013;32:1–12.
61 Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 2015;1: CD004376.
62 Bartels EM, Juhl CB, Christensen R, Hagen KB, Danneskiold-Samsøe B, Dagfinrud H, et al. Aquatic exercise for the treatment of knee and hip osteoarthritis. Cochrane Database Syst Rev 2016;3:CD005523.
63 Batsis JA, Germain CM, Va´squez E, Zbehlik AJ, Bartels SJ. Physical activ ity predicts higher physical function in older adults: the osteoarthritis initiative. J Phys Act Health 2016;13:6–16.
64 Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, DeVita P, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA 2013;310:1263–73.
65 White DK, Keysor JJ, Neogi T, Felson DT, LaValley M, Gross KD, et al. When it hurts, a positive attitude may help: association of positive affect with daily walking in knee osteoarthritis. Results from a multicenter lon gitudinal cohort study. Arthritis Care Res (Hoboken) 2012;64:1312–9.
66 Van den Berg WB. Pathophysiology of osteoarthritis. Joint Bone Spine 2000;67: 555–6.
67 Martel-Pelletier J. Pathophysiology of osteoarthritis. Osteoarthr Cartil 2004;12(Suppl A):S31–3.
68 Glyn-Jones S, Palmer AJ, Agricola R, Price AJ, Vincent TL, Weinans H, et al.Osteoarthritis. Lancet 2015.
69 Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. Nat Rev Rheumatol 2015.
70 Karsdal MA, Christiansen C, Ladel C, Henriksen K, Kraus VB, Bay-Jensen AC. Osteoarthritis—a case for personalized health care? Osteoarthr Cartil 2014; 22:7–16.

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Diagnosis and Clinical Presentation of Osteoarthritis

KEYWORDS : Osteoarthritis Clinical features Differential diagnosis

KEY POINTS :

- Osteoarthritis (OA) has a marked variability of clinical presentation and prognosis.
- OA targets specific joints (eg, knees, hips, finger IPJs, thumb bases, first metatarsopha- langeal joints, and spinal facet joints).
- Frequent symptoms and signs include usage-related joint pain, morning-related or inactivity-related stiffness of short duration, locomotor restriction, coarse crepitus, bony enlargement, and joint-line tenderness.
- Rest pain, night pain, and deformity suggest severe OA.
- Painful periarticular soft tissue disorders frequently coexist with knee, hip, and first meta- tarsophalangeal OA.
- The diagnosis of OA may be reached without any laboratory or radiographic investigations in the at-risk population in the presence of typical signs and symptoms.
- Associated calcium pyrophosphate and basic calcium phosphate crystal deposition is common, especially in the elderly, and may be associated with inflammatory symptoms and signs.

1. INTRODUCTION

Osteoarthritis (OA) is a condition of synovial joints that represents failed repair of joint damage that results from stresses that may be initiated by an abnormality in any of the synovial joint tissues.1 OA may be localized to [1] joint, to a few joints, or be general- ized.1 It is the commonest arthropathy, and presents with joint pain, locomotor restric- tion, and varying degrees of functional impairment.[2,3] It has a marked variability of phenotypic expression. The age of onset, pattern of joint involvement, and rate of progression vary from person to person and from site to site. For example, OA may be an asymptomatic incidental finding on clinical or radiographic examination, or be a progressive, painful, and disabling disorder at different joints in the same person. Thus there is an imperfect overlap between the disease OA (structural changes visu- alized on imaging) and the illness OA (patients' reported symptoms).[1] This article describes the clinical features of OA with an emphasis on symptoms and signs at the key target sites.

CLINICAL FEATURES

Pain, stiffness, and locomotor restriction are the main symptoms of OA (Table 1).[3] Other symptoms include crepitus, joint deformity, or joint swelling (caused by bony remodeling, excessive osteophytosis, or joint subluxation). These symptoms typically begin in just 1 or a few joints in a person of middle or older age. Pain worse with joint use and relieved by rest (usage or mechanical pain) is often the most troublesome symptom. The origin of pain in OA is not completely understood. Pain may arise from the nociceptive fibers and mechanoreceptors in the synovium, subchondral bone, periosteum, capsule, tendons, or ligaments. Pain in large joint OA (eg, knee or hip) is also thought to arise from bone marrow lesions, and synovitis/ effusion by stimulation of nociceptive fibers and intra-articular hypertension, respectively,[4,5] and a similar mechanism may also operate in the small joints. However, hyaline cartilage is aneural, and is not a source of pain in OA. Whatever its source, both central and peripheral sensitization perpetuate and amplify pain in OA. Pain generally progresses through 3 stages (Table 2).[6] However, pain progression may be arrested at any stage, and not all patients go through 3 distinct stages.

Temporal and seasonal variations in OA pain have been reported as for other arthropathies. Pain in OA is reported to be worst on waking up in the morning, with an improvement in the next 2 hours.[7] It then worsens in the late afternoon/early evening to again reduce later in the evening.[7] However, night pain can be present in OA, which interferes with sleep and leads to fatigue, lack of well-being, and increased pain sensitivity. Such non-usage night pain is thought to arise largely from the subchondral bone. In some people, the pain has a burning (neuropathic) quality, is widespread around the joint, and associates with tenderness and paresthesiae.[6] Such features also suggest comorbid fibromyalgia, another common pain syndrome in older people.

Painful periarticular soft tissue lesions may coexist with large joint OA[8] (eg, pes- anserine bursitis, greater trochanter pain syndrome) and it may be difficult to identify the cause of the pain. One solution to this problem is to ask the patient to point to the most painful area and then to map out the area that feels uncomfortable. Periarticular soft tissue lesions cause localized pain away from the joint line, whereas OA pain more commonly is most severe over the joint line except for proximal joints (hip, shoulder), which may have the maximal site of pain distal to the originating joint (radiated pain).

Stiffness is also common in OA. Stiffness may be thought of as a difficulty or discomfort during movement caused by a perceived inflexibility of the joint. Stiffness is usually most noticeable early in the morning, but may also occur later in the day, typically after periods of inactivity. Early morning stiffness is present both in classic inflammatory arthritis (eg, rheumatoid arthritis [RA]), and in OA. It can be considered an inflammatory symptom when prolonged and present for at least 30 minutes before maximal improvement. The morning stiffness in OA is typically short lived (usually a few minutes, but in general <30 minutes). Short-lived stiffness (gelling) may also be brought on by inactivity. In pa

tients with OA, both morning and inactivity-related stiffness quickly improve and resolve with joint use, whereas the joint pain subse- quently worsens with continued use.

Locomotor restriction and the resulting functional impairment depend on the site and severity of OA. For example, first carp metacarpal joint (CMCJ) OA may cause difficulty in gripping, whereas knee or hip OA may impair the ability to get up from a chair and walk. The resulting participation restriction depends on the individual's daily activities and occupational/recreational requirements.

The main physical signs of OA are coarse crepitus, joint-line tenderness, bony swelling, deformity, and reduced range of movement.

Crepitus is a coarse crunching sensation or sound caused by friction between damaged articular cartilage and/or the bone. It may be more prominent during active movement than during passive movement during physical examination. It is often present throughout the range of movement.[9] Crepitus may be exacerbated by stress- ing the joint surfaces (eg, patellofemoral joint [PFJ] crepitus is increased by applying downward pressure on the patella with the examining hand during knee flexion).[10] Transmitted crepitus (felt on the adjacent periarticular bone) suggests a full- thickness cartilage defect on the affected side.[10]

Tenderness in and around the joint is common in OA. Joint-line tenderness suggests

Key points

- Painful periarticular soft tissue lesions may coexist with large joint OA (eg, pes- anserine bursitis, greater trochanter pain syndrome) and it may be difficult to identify the cause of the pain. One solution to this problem is to ask the patient to point to the most painful area and then to map out the area that feels uncomfortable.

Table 1
Principal manifestations of OA

Symptoms	
Joint pain	Usually affects 1 to few joints at a time Insidious onset: slow progression over months to years Variable intensity throughout the day and the week May be intermittent and relapsing Increased by joint use and impact Relieved by rest Night pain may occur in severe OA
Stiffness	Short-lived (<30 min) early morning stiffness Short-lived inactivity-related stiffness (gelling)
Swelling	Some (eg, nodal OA) patients present with swelling and/or deformity
Age	>40 y[a]
Constitutional symptoms (eg, weight loss, sweats, fever)	Absent
Signs	
Appearance	Swelling (usually bony ± fluid/soft tissue) Resting position (attitude) Deformity Muscle wasting (global: all muscles acting over the joint)
Feel	Absence of warmth Swelling: bony or effusion Effusion if present is usually small and cool Joint-line tenderness Periarticular tenderness (especially knee, hip)
Movement	Coarse crepitus [b] Reduced range of movement Weak local muscles

[a] Major joint injury and certain rare conditions may predispose to OA before the age of 40 years.
[b] Audible crepitus may be a symptom of knee OA.
Adapted from Abhishek A, Doherty M. Disease diagnosis and clinical presentation. In: Henrotin Y, Hunter DJ, Kawaguchi H, editors. OARSI Online Primer. OARSI; 2011.

Table 2
Stages of pain in OA

Stage 1 (Early)	Predictable sharp pain, usually brought on by a mechanical insult that eventually limits high-impact activities. There may only be a minimal effect on function.
Stage 2 (Mild-moderate)	Pain becomes a more regular feature, and begins to affect daily activities. There may be unpredictable episodes of stiffness.
Stage 3 (Advanced)	Constant dull/aching pain, punctuated by short episodes of often unpredictable intense, exhausting pain that results in severe functional limitations.

Key points

- Pain, stiffness, and locomotor restriction are the main symptoms of OA. Other symptoms include:
- Crepitus
- Joint deformity or joint swelling caused by-
  - o Bony remodeling
  - o Excessive osteophytosis
  - o Joint subluxation
- These symptoms typically begin in just 1 or a few joints in a person of middle or older age. Pain worse with joint use and relieved by rest (usage or mechanical pain) is often the most troublesome symptom. The origin of pain in OA is not completely understood.
- Pain may arise from the nociceptive fibers and mechanoreceptors in the synovium, subchondral bone, periosteum, capsule, tendons, or ligaments. Pain in large joint OA (eg, knee or hip) is also thought to arise from bone marrow lesions, and synovitis/effusion by stimulation of nociceptive fibers and intra-articular hypertension, respectively, and a similar mechanism may also operate in the small joints.

an articular disorder, whereas tenderness away from the joint line suggests a periarticular soft tissue disorder. Both joint-line and periarticular tenderness may be present simultaneously because of a high frequency of periarticular soft tissue disorders near joints with OA. Reduced range of movement (equal for both active and passive movements) mainly results from marginal osteophytosis and capsular thickening, but synovial hyperplasia and effusion also contribute. Fixed flexion deformities (the inability to fully extend the joint) occurs at the knees, hips, or elbows in advanced severe OA. Bony swelling, which may be evident in both small (eg, IPJ, first metatar- sophalangeal) and large (eg, knee) joint OA, occurs because of a combination of bony remodeling, marginal osteophytosis, and joint subluxation. Deformity and instability are signs of marked joint damage. Muscle wasting suggests advanced OA.

HOLISTIC ASSESSMENT

Patients with OA should be assessed in a ta geted manner for depression, sleep deprivation, hyperalgesia, central sensitization, and catastrophization.[11–14] Each of these has the potential to increase the pain sever ty. An attempt must similarly be made to assess the presence of joint pain at other sites as it increases pain severity at the index joint.[15] Mobility assessment and neuromu cular examination should be per- formed for patients with suspected hip or knee OA because these both associate with muscle weakness, impaired joint position sense, and falls.16 The risk of falls may be further increased by postural hypotension, visual or vestibular impairment, and polypharmacy, which are common in the elderly. Fibromyalgia is another common comorbidity in the elderly and should be considered and sought (by examination for widespread hyperalgesic tender sites) in anyone presenting with musculoskeletal pain, especially if they report nonrestorative or nonrefreshing sleep. Adverse risk factors (Box 1) should be sought and considered in the management plan. In addition, illness perceptions regarding joint pain and OA should be explored and discussed with the patient because these may influence treatment adherence and outcome.[17]

ROLE OF INVESTIGATIONS

OA is a clinical diagnosis. It may be diagnosed without recourse to laboratory or radio-graphic investigations in the presence of typical symptoms and signs in the at-risk age group.[2,22,23] Peripheral joint OA may be diagnosed confidently on clinical grounds alone if there is:

- Persistent usage-related joint pain in 1 or a few joints
- Age 45 years
- Only brief morning stiffness (30 minutes).[2]

Other features listed in Table 1 add to the diagnostic certainty.[2] This approach to a clinical diagnosis of OA is supported by the poor correlation between radiographi- cally assessed structural changes and symptoms in OA.[24] The American College of Rheumatology (ACR) clinical classification criteria for knee, hip, and hand OA have a high sensitivity, and at least a moderate to high specificity for discriminating OA from other rheumatic conditions in a hospital setting.[9,25,26] However, the ACR criteria are not diagnostic, and failure to meet the clas-

Box 1
Risk factors for poor prognosis in OA

Age

Obesity

Knee malalignment (varus-valgus), hindfoot malalignment

Lower limb length inequality (≥1–2 cm)

Presence of OA in multiple joints (eg, generalized OA [GOA])

Excess or no joint use

Muscle wasting and weakness

Joint laxity

Poor mental health, lack of self-efficacy, and poor social support (for worsening symptoms only)

Data from Refs. [18–21]

sification criteria does not exclude OA. They also have a low sensitivity and specificity for classifying mild-moderate OA in the community setting.[27] However, appropriate imaging and laboratory assessments should be performed:

- In younger individuals (ie, <45 years in age) in the absence of preceding major joint trauma,
- If symptoms and signs are atypical; for example, not usual target sites for OA, symptoms and signs of significant joint inflammation, marked rest and/or night pain, rapidly progressive pain,
- If there is weight loss or constitutional upset,
- If there is true locking at the knee, which suggests additional mechanical derangement.

Inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, plasma viscosity) are normal or only minimally increased in OA, and may be useful in excluding other diagnoses. Radiographic examination may be used to support a clinical diagnosis of OA. However, patients with a clinically robust diagnosis of OA may have normal radiographs, and vice versa. Thus, radiographic examination should not be used to establish a diagnosis of OA by itself, and neither should a normal plain radiograph be used to refute a clinical diagnosis of OA; 86% of middle-aged community-dwelling residents (mean age 45 years) with knee pain for more than 3 months develop radiographic knee OA over the next 12 years, suggesting that knee pain may be the first sign of OA.[28] However, such patients should be examined carefully to exclude any other cause of joint pain, such as periarticular soft tissue lesions, before arriving at a diagnosis of OA and more sensitive examination of the joint (eg, ultrasound or magnetic resonance imaging) may be warranted. However, radiographic examination may have a role in defining the prognosis of patients with OA. In a prospective study of more than 1507 patients with knee OA, those with more severe joint space narrowing at baseline progressed more rapidly to complete joint space loss over time than those with no joint space narrowing at baseline.[29] Global OA severity had a similar but smaller role.[29] In summary, OA may be diagnosed on clinical grounds alone in the at-risk population, with radiographs being used more for prognostic than diagnostic purposes.

Synovial fluid examination is not routinely required to support a diagnosis of OA. However, joint aspiration and synovial fluid analysis are indicated if there is a suspicion of coexistent crystal deposition. Both monosodium urate and calcium pyrophosphate (CPP) crystal deposition (CPPD) associate with OA and may cause acute synovitis or more

Key points

- OA is a complex condition and that disease onset may be triggered by pathology in multiple tissues. Therefore, there is no single drug that can be used for the treatment of all OA patients. A drug that inhibits the structural disease progression of OA with symptomatic relief was defined as a disease modifying osteoarthritis drug (DMOAD).
- Fibroblast growth factor 18 (FGF-18) binds to its receptor in cartilage and stimulates chondrogenesis and cartilage matrix production. Sprifermin is a synthetic form of human FGF-18. A randomized, double-blind, placebo-controlled, proof-of-concepttrial was conducted in 180 patients with symptomatic knee OA.

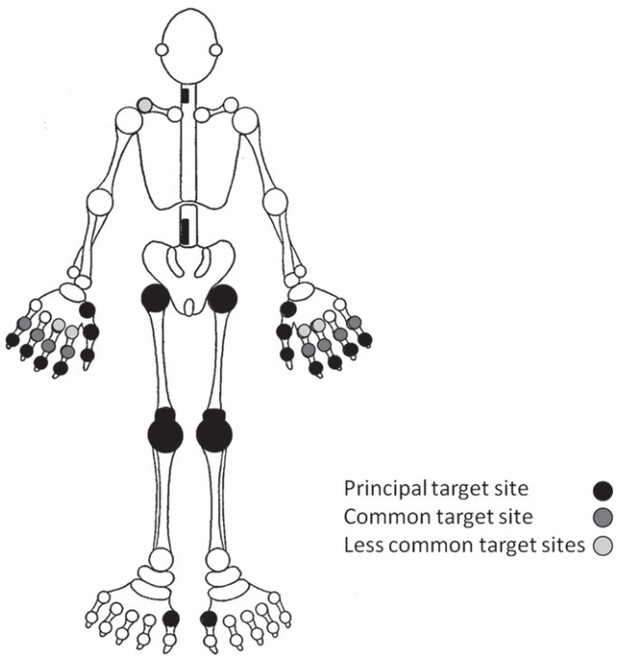


Fig. 1. Joints targeted by OA. (Reproduced from Abhishek A, Doherty M. Disease diagnosis and clinical presentation. In: Henrotin Y, Hunter DJ, Kawaguchi H, editors. OARSI Online Primer. OARSI; 2011; with permission.)

Key points

- Stiffness is also common in OA. Stiffness may be thought of as a difficulty or discomfort during movement caused by a perceived inflexibility of the joint. Stiffness is usually most noticeable early in the morning, but may also occur later in the day, typically after periods of inactivity. Early morning stiffness is present both in classic inflammatory arthritis (eg, rheumatoid arthritis [RA]), and in OA.
- It can be considered an inflammatory symptom when prolonged and present for at least 30 minutes before maximal improvement. The morning stiffness in OA is typically short lived (usually a few minutes, but in general <30 minutes).
- Short-lived stiffness (gelling) may also be brought on by inactivity. In patients with OA, both morning and inactivity-related stiffness quickly improve and resolve with joint use, whereas the joint pain subsequently worsens with continued use.

chronic inflammation in OA joints. Community-based studies suggest that coexistent self-reported gout and OA of the knee and hip occur in 1.1% and 0.8% of patients older than 25 years, respectively,[30] whereas coexistent knee chondrocalcinosis (a marker of CPPD) and knee OA occur in 2.4% of patients older than 40 years.[31] Basic calcium phosphate (BCP) crystal deposition is also common in OA but requires sophisticated techniques (eg, scanning electron microscopy) for accurate identification, and its presence is not sought routinely.

DISTRIBUTION OF JOINTS AFFECTED BY OA

OA can affect any synovial joint. However, it targets the knees, hips, first CMCJs, finger IPJs, first metatarsophalangeal (bunion) joints (first metatarsophalangeal joints [MTPJs]) and apophyseal (facet) joints of the lower cervical and lower lumbar spine (Fig. 1).[32]

CLASSIFICATION

OA can be classified according to the nu ber of affected joints, presumed cause, age of onset, radiographic appearance (hypertr phic vs atrophic), presence of calcium crystals, and rate of progression. Several classif cation systems have been proposed. Each has its own strengths and weaknesses. We present a simplified system adapted from the original ACR classification9 and that is possibly better suited for clinical use (Box 2).

GOA

Although it was recognized earlier, Kellgren and Moore[33] described a polyarticular subset of OA particularly involving the distal IPJs (DIPJs), thumb bases (first CMCJs and trapezioscaphoid joints), first MTPJs, facet joints, knees, and hips, and coined the term GOA for this subset. GOA is characterized by a slow accumulation of multiple joint i volvement (compared with RA, which us ally affects multiple joints synchronously). Symptoms usually commence in the hand

Box 2
Simplified clinical approach to identifying OA subsets

1. Number ofjoints involved
   a. Localized: 1–2 joint regions involved only (specify location)
   b. GOA: ≥3 joint regions involved, with spine/hands being one of the regions affected (nodal GOA if nodes present)
2. Classic or atypical OA (atypical OA: unusual distribution, young age of onset [<45 years], rapid progression)

Causes of atypical OA include:

a. Prior trauma (common): mainly monoarticular or oligoarticular OA, young onset, often with a clear history ofinjury
b. Dysplasia:
   i. Localized (eg, hip): childhood or young adult onset
   ii. Polyarticular (eg, spondyloepiphysial dysplasia): young onset, short stature, morphologic features, and a positive family history may be present
c. Childhood arthropathy or derangement: eg, juvenile idiopathic arthritis, Perthes disease and slipped femoral epiphysis of hip, septic arthritis
d. Metabolic or endocrine diseases: eg, hemochromatosis, which mainly targets metacarpophalangeal joints (MCPJs), wrists, hips, and may be of young onset, mainly in men; acromegaly, which has typical signs of OA with little restriction in movements, hypermobility
e. Late avascular necrosis: predominantly hips, shoulders, and knees, more rapid progression, risk factors present (eg, steroid use)
f. Neuropathic joints: rapid clinical progression, marked joint disorganization
   i. Hindfoot, midfoot: diabetes mellitus
   ii. Shoulders, elbows, wrists: syringomyelia
g. Apatite-associated destructive arthritis: old age, rapid progression; targets hips, knees, and shoulders

3. Clinical joint inflammation: usually absent; if present, consider:
   a. Crystal deposition: CPPD and gout (OA encourages deposition of both crystal types)
   b. Coexistent inflammatory arthritis: eg, RA, seronegative spondyloarthropathy
   c. Erosive OA: targets hand IPJs

Modified from Abhishek A, Doherty M. Disease diagnosis and clinical presentation. In: Henrotin Y, Hunter DJ, Kawaguchi H, editors. OARSI Online Primer. OARSI; 2011.

Key points

- Locomotor restriction and the resulting functional impairment depend on the site and severity of OA. For example, first carp metacarpal joint (CMCJ) OA may cause difficulty in gripping, whereas knee or hip OA may impair the ability to get up from a chair and walk. The resulting participation restriction depends on the individual's daily activities and occupational/recreational requirements.

joints around middle age and affect the knees and other joints over the next few decades. The clinical marker for GOA is the presence of multiple Heberden nodes, which are po terolateral hard swellings of the DIPJs, associated with underlying OA.[33] Heberden nodes are often accompanied by less well-defined posterolateral swellings of the proximal IPJs (PIPJs): so-called Bouchard nodes. A form of GOA showing identical joint targeting was subsequently identified in patients without Heberden nodes,[34] which led to GOA being classified as nodal and non-nodal forms,[34] the former being more common in women, and the latter mainly occurring in men.[35] There is no universal definition of the number of joints that must be affected before an individual can be diagnosed as having GOA. However, guidance from ACR and The Eropean League Against Rheumatism suggests that GOA is present if there is OA at the spine or hand, and in at least 2 other joint regions.[9,23]

CLINICAL FEATURES AT THE MAIN SYMPTOMATIC SITES

Hands

Hand OA is usually bilaterally symmetric.[23,26] Symptoms affect just 1 or a few joints at a time.[23] Symptoms are often intermittent and occur at the target sites, namely DIPJs (w50%), thumb bases (w35%), PIPJs (w20%), and MCPJs (w10%), in descending order of frequency.[23,36] Individuals without pain may report a dull ache or stiffness.[26] The symptoms of hand OA deteriorate in half the patients over the next 6 years.[37] The predictors of a worse clinical outcome include a high level of functional impairment at baseline and a greater number of painful joints, with no correlation between clinical change and radiographic progression.[37]

Nodal OA

Heberden and/or Bouchard nodes plus underlying IPJ OA (defined clinically and/or radiologically) constitutes nodal OA.[23] It affects women more frequently than men, and familial predisposition is recognized. Symptoms usually start in middle age, often around the menopause, with pain, tenderness, and stiffness of 1 or a few DIPJs in the hands. There may be warmth and soft tissue swelling at the start. Over a period of months or years, involved IPJs usually become less painful and signs of inflammation subside, leaving behind firm to hard bony swellings on the posterolateral aspect of the IPJs, termed Heberden (DIPJ) and Bouchard (PIPJ) nodes (Fig. 2). Over the next decade or so, other IPJs go through the same process, in a monoarthritis multiplex manner. Established DIPJ (or PIPJ) nodes sometimes coalesce to form a single dorsal bar (see Fig. 2). In addition to bony swelling, the affected IPJs commonly deviate laterally (radial or ulnar, with most deviations pointing toward the middle finger) and have reduced range of movement. Lateral deviation at the IPJs without IPJ instability is a characteristic feature of nodal OA (Fig. 3). Nodal OA is most common at the index and middle fingers.[26] Fully evolved nodes are not painful, and usually associate with a good long-term functional outcome. However, some patients are concerned by the cosmetic aspect of these deformities.

The thumb base, comprising the first CMCJ and trapezioscaphoid joint, is another target site for OA. Thumb base OA presents with pain on joint use at the thumb base area with some distal and proximal radiation. There may be radial subluxation of the metacarpal base or adduction at the thumb base, giving it a swollen, squared appearance (Fig. 4).[23,26] Unlike IPJ OA, thumb base OA associates with persistent symptoms and with greater functional impairment (occasionally requiring surgery), so the prognosis is generally worse.

OA mainly targets the second, third, and first MCPJs, in descending order of frequency, often causing bony enlargement without signs or symptoms of synovitis.[36] Isolated MCPJ OA sometimes occurs in elderly people who have had physically demanding occupations (Missouri arthritis).[38] Widespread MCPJ changes, especially with wrist arthropathy or chondrocalcinosis, suggest the possibility of hemochromatosis.

Erosive OA

Erosive OA is an aggressive subset of hand OA. It presents with subacute or insidious onset of pain, stiffness, soft tissue swelling, and sometimes paresthesia affecting multiple IPJs (synchronous polyarticular onset).[23,39] Pain, tenderness, inflammation (warmth, soft tissue swelling, sometimes erythema) are more marked and prolonged compared with nodal hand OA[39,40] and there is no association with GOA. Erosive OA usually spares the thumb base and MCPJs[23] and

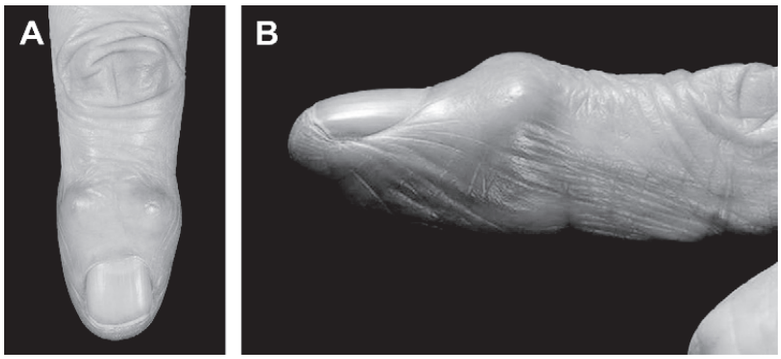


Fig. 2. (A) Heberden nodes appearing as discrete posterolateral swelling over the DIPJs, and (B) coalescing to form a single dorsal bar.

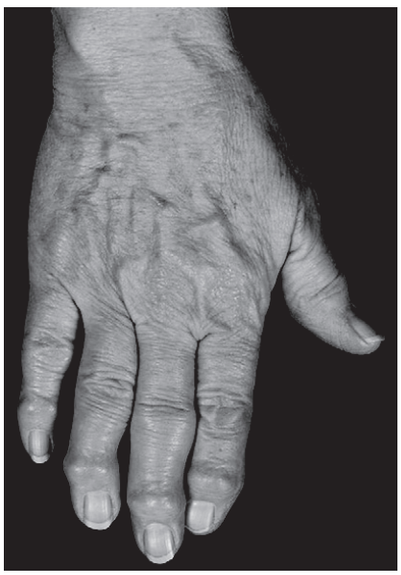
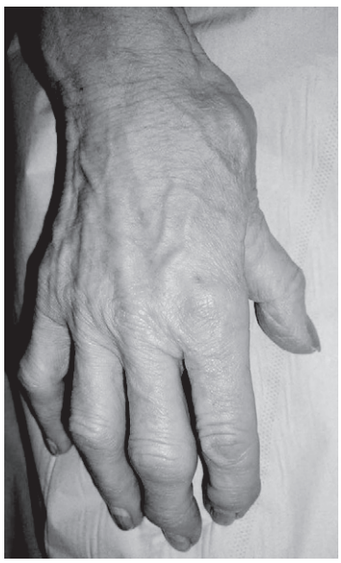


Fig. 3. Heberden nodes and lateral deviation of IPJs in nodal OA.



b base OA: squaring of the thumb base, caused by osteopł st carpometacarpal joint.

Key points

- The main physical signs of OA are:
  - o Coarse crepitus
  - o Joint-line tenderness
  - o Bony swelling
  - o Deformity
  - o Reduced range of move ment

targets DIPJs more commonly than PIPJs (Fig. 5).[40] Lateral instability and ankylosis at the IPJs are uncommon but characteristic clinical findings in erosive OA (Fig. 6). There may rarely be an operaglass deformity,40 and Heberden, and/or Bouchard nodes may coexist.[41] Erosive OA is defined radiographically by subchondral erosion, cortical destruction, marked bone and cartilage attrition, and subsequent reparative change that may include bony ankylosis. It has a worse outcome in terms of symptom persistence and functional impairment than nonerosive hand OA.[23] Although erosive OA as a clinical entity is rare, radiographic erosions are present in 1 or a few joints in up to 8.5% of patients with symptomatic hand OA.[42] The differential diagnosis for hand OA is wide, and includes:

- Psoriatic arthritis: targets DIPJs or affects just 1 ray
- RA: targets wrists, MCPJs, PIPJs
- Gout: may be superimposed on preexisting hand OA
- Hemochromatosis: mainly targets MCPJs, and wrists[23]

OA at Other Upper Limb Joints

OA may be present in the other upper limb joints, especially in the presence of occup tional risk factors. For example, people with mechanically demanding jobs can develop elbow, shoulder, wrist, and acromioclavic lar joint OA. Shoulder (glenohumeral joint) OA may also be a consequence of, or ass ciate with, rotator cuff tear. The symptom at these joints is as for OA in other joints (see Table 1) and is most commonly unilateral.

Knee

The knee is an important target site for OA. Knee OA alone is the commonest cause of lower limb disability in elderly people. It is usually bilateral, although symptoms may be more pronounced on 1 side. Unilateral knee OA is more common in young men, and is often caused by prior knee injury or surgery. Most patients with knee OA have medial compartment tibiofemoral joint (TFJ) OA, PFJ OA, or a combination of both.[43,44]

Knee joint pain is felt anteriorly and the lcation and pattern of pain indicate the affected compartment(s). Pain is anteromedial in medial compartment TFJ OA, and anterior and behind the patella in PFJ OA.[45] Pain from PFJ OA is typically worsened by prolonged sitting, standing up from low chairs, and climbing stairs or inclines (coming down often being more painful than going up). Generalized knee pain with distal radiation suggests moderate to severe knee OA.[46] Per-

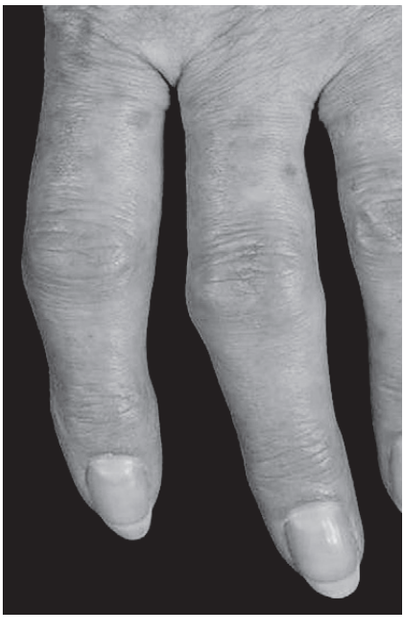


Fig. 5. Erosive OA: marked radial deviation and fixed flexion deformity in the left middle PIPJ, radial deviation with restriction in the index PIPJ, and bony swelling of both fingers. Note the absence of Heberden nodes. (Reproduced from Abhishek A, Doherty M. Disease diagnosis and clinical presentation. In: Henrotin Y, Hunter DJ, Kawaguchi H, editors. OARSI Online Primer. OARSI; 2011; with permission.)

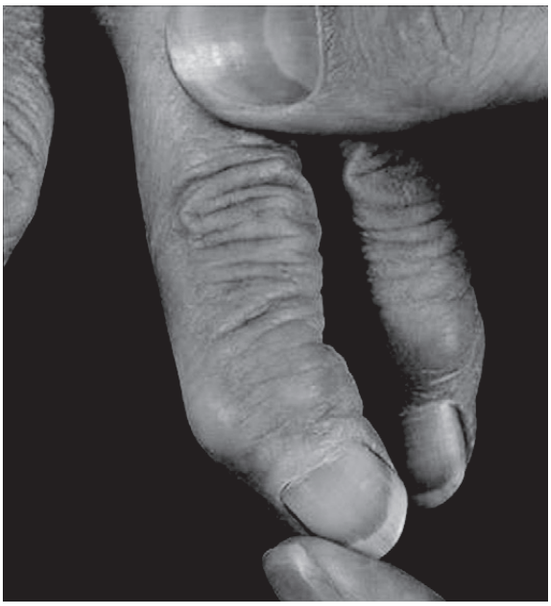


Fig. 6. Erosive OA: marked radial/ulnar instability. Such instability does not usually occur with the common hand OA. (Reproduced from Abhishek A, Doherty M. Disease diagnosis and clinical presentation. In: Henrotin Y, Hunter DJ, Kawaguchi H, editors. OARSI Online Primer. OARSI; 2011; with permission.)

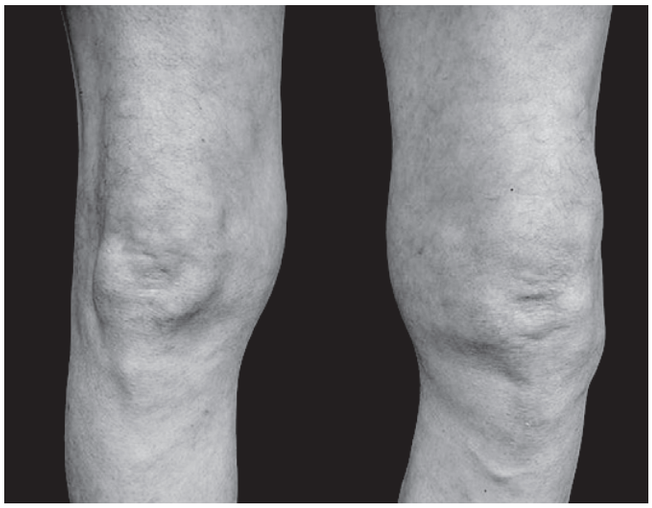


Fig. 7. Unilateral knee OA: swollen left knee with varus and fixed flexion deformities in a 63-year-old man with a history of knee trauma. On palpation there was marked crepitus, restricted flexion, bony swelling, and a small effusion. The cruciates were intact but there was minor varus/valgus instability on stress testing. (Reproduced from Abhishek A, Doherty M. Disease diagnosis and clinical presentation. In: Henrotin Y, Hunter DJ, Kawaguchi H, editors. OARSI Online Primer. OARSI; 2011; with permission.)

Key points

- OA is a clinical diagnosis. It may be diagnosed without recourse to laboratory or radio-graphic investigations in the presence of typical symptoms and signs in the at-risk age group. Peripheral joint OA may be diagnosed confidently on clinical grounds alone if there is:
- Persistent usage-related joint pain in 1 or a few joints
- Age 45 years
- Only brief morning stiffness (30 minutes)

sistent OA.[46] Persistent rest and night pain occur in advanced OA.[22] Knee OA symptoms usually do not cause posterior knee pain unless there is a complicating popliteal (Baker) cyst. Apart from pain, there may be a feeling of giving way (especially with PFJ OA and/or quadriceps weakness) and instability, both of which associate with falls.[22]

On examination, the findings are typical of OA (see Table 1). Tibiofemoral joint-line tenderness is felt anteriorly, on either side of the patella tendon with the knee flexed. Pain on patellofemoral compression, deformity (fixed flexion and/or varus; less commonly valgus deformity on weight bearing), quadriceps wasting and weakness, and hip muscle weakness may be present (Fig. 7).[22,47,48] Knee effusion is common, and increases in prevalence with the severity of knee OA. For example, in a study, 36% of patients with symptomatic knee OA (Kellgren and Lawrence [K&L] score [2]) had a clinical knee effusion, whereas only 16% of symptomatic preradiographic knee OA (magnetic resonance imaging cartilage score[2], and K&L score[2]) had clinically detectable knee effusion.[49] Several painful periarticular soft tissue disorders coexist with knee OA and require careful assessment (Table 3).[8,50,51]

Hip

Hip OA presents with pain, stiffness, and rstricted movement. Pain caused by hip OA is usually maximal deep in the anterior groin, but may spread to the anteromedial or upper lateral thigh, and occasionally the buttocks. Distal radiation is common, and pain may predominate at the knee. Some people present with knee pain without any proximal pain; unlike knee-originated pain, such hip-referred pain is usually more generalized, involves the distal thigh, and may be improved by rubbing. Pain in hip OA is exacerbated by rising from a seated position, and during initial or midambulation.[25] It may be difficult to differentiate hip OA pain from referred spinal pain or concomitant knee OA,[25] and intra-articular local anesthetic injection may be required to reso

Table 3
Common periarticular lesions that coexist with knee OA

Soft Tissue Disorder	Signs and Symptoms
Anserine bursitis	Inferomedial knee pain, localized soft tissue swelling (rarely), tenderness over the upper medial tibia
Semimembranosus-tibial collateral ligament bursitis	Medial knee pain, tenderness closer to the joint line than in anserine bursitis
Medial collateral ligament (inferior insertion) enthesopathy	Medial knee pain, localized tenderness, and pain on stressing the medial ligament (valgus strain with knee unlocked)
Tender medial fat pad	Medial knee pain, tenderness over either the inferior or superior fat pad below or above the joint line
Iliotibial tract (band) syndrome	Lateral distal thigh and knee pain, and tenderness maximal over the lateral femoral condyle

-lve any diagnostic uncertainty.[52] Unlike knee OA, hip OA is often unilateral.[53]

Both active and passive hip movements may be painful.[25] Internal rotation with the hip flexed is frequently the earliest movement to be restricted, but movements may be globally restricted in severe disease (Fig. 8).[25] The typical end-stage deformity in hip OA is external rotation, adduction, and fixed flexion (Fig. 9). Wasting of thigh muscles, positive Trendelenburg test, antalgic gait, and shortening of the affected extremity may also be present.[25] However, such end-stage hip OA should be rare in modern clinical practice.

Hip OA may be subclassified largely according to radiographic features, specifically[54,55]

1. Pattern of radiographic femoral head migration
   a. Superior: most usual pattern (especially in men), likely to be uni lateral at presentation and to progress more rapidly
   b. Axial (along the axis of the fem oral neck): progresses more slowly
   c. Medial: mainly in women, likely to be bilateral and associate with Heberden nodes
2. Bone response to joint space loss
   a. Atrophic: characterized by marked bone attrition and mini mal osteophytosis, common in el derly, associated with chondrocal cinosis
   b. Hypertrophic: characterized by florid osteophytosis.

In some patients, especially elderly women, hip OA can be rapidly progressive with a subacute onset of symptoms that progresses to joint destruction and instability in a matter of months rather than years. The radiographs may show paradoxic widening of joint space (although this is reduced or absent if standing or stressed films are taken), marked bone attrition, destruction of the femoral head, and paucity of osteophytosis (atrophic OA).[56] Such rapidly progressive destructive arthropathy has been associated with BCP (mainly hydroxyapatite) crystals, and termed apatiteassociated destructive arthropathy (AADA).[57–59] Shoulders (Milwaukee shoulder)[60] and knees are other target sites for AADA. Muscle wasting, deformities, and moderate to large joint effusions with noninflammatory (viscous, occasionally hemorrhagic, low cell count) synovial fluid are common.

Several other disorders may lead to pain around the hip region.[61] For example, anterior groin pain may be caused by osteonecrosis (avascular necrosis) of the femoral head.[61] With this, pain is initially usually night predominant, well localized, unrelated to usage and progressive, becoming worse on usage and more widespread once the femoral bone and overlying cartilage col

Key points

- Inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, plasma viscosity) are normal or only minimally increased in OA, and may be useful in excluding other diagnoses. Radiographic examination may be used to support a clinical diagnosis of OA. However, patients with a clinically robust diagnosis of OA may have normal radiographs, and vice versa.
- Thus, radiographic examination should not be used to establish a diagnosis of OA by itself, and neither should a normal plain radiograph be used to refute a clinical diagnosis of OA; 86% of middle- aged community-dwelling residents (mean age 45 years) with knee pain for more than 3 months develop radiographic knee OA over the next 12 years, suggesting that knee pain may be the first sign of OA.

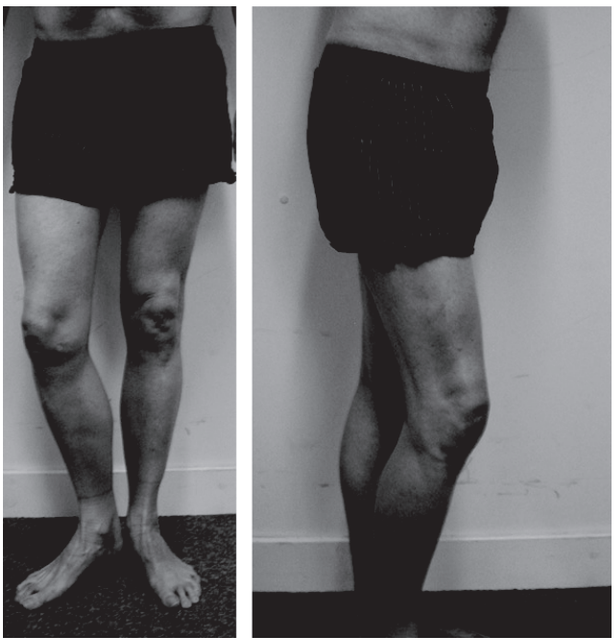


Fig. 8. Patient with right hip OA showing fixed flexion and external rotation deformity. (Reproduced from Abhishek A, Doherty M. Disease diagnosis and clinical presentation. In: Henrotin Y, Hunter DJ, Kawaguchi H, editors. OARSI Online Primer. OARSI; 2011; with permission.)

Fig. 9. Patient with hip OA, showing painful restriction in internal rotation in flexion: the tight-pack position for the hip and the first movement to be affected. (Reproduced from Abhishek A, Doherty M. Disease diagnosis and clinical presentation. In: Henrotin Y, Hunter DJ, Kawaguchi H, editors. OARSI Online Primer. OARSI; 2011; with permission.)

lapse to result in arthropathy. Posterior hip and buttock pain may be caused by lumbar radiculopathy, iliolumbar ligament syndrome, sacroiliac joint pain, and hip extensor or rotator muscle strain.[61] Other periarticular disorders that may coexist with hip OA are listed in Table 4.

Facet Joint OA

It is often difficult to attribute symptoms to facet joint OA because it commonly coexists with intervertebral disk degeneration. However, lumbar facet joint OA is thought to lead to localized lumbar pain, which may radiate unilaterally or bilaterally to the buttocks, groins, and thighs, typically ending above the knees.[62] Symptoms are worse in the morning and during periods of inactivity, and are increased by stress, exercise, lumbar spine extension, rotary motions, and when standing or sitting.[62] Lying flat and flexion of the lumbar spine lead to pain relief.[62] Cervical facet joint OA similarly may present with ipsilateral neck pain that does not radiate beyond the shoulder, and is worsened by neck rotation or extension.[63] The osteophytes in facet joint OA may also impinge on nerve roots and lead to radiculopathy.

First MTPJ OA

First MTPJ OA is usually bilateral, and when symptomatic, causes localized big toepain mainly on standing and during ambulation. Bony enlargement of the first MTPJmay be present (Fig. 11). Hallux valgus (distal end of big toe points toward the midlineof the foot), hallux rigidus (restricted flexion, and extension at the first MTPJ), and crossover toes are the other common deformities. Bony enlargement at the first MTPJ and hallux valgus frequently lead to the development of a complicating bursa with additional fibrous tissue reaction on the medial aspect of the first MTPJ (bunion; Fig. 10). This joint may get inflamed (eg, by rubbing against footwear) and cause medial big toe pain. Apart from the first MTPJ, OA also commonly targets the talonavicular joint in the midfoot (aggravated by pes planus; see Fig. 11), and sometimes the ankle and subtalar joints in the hindfoot (especially in those with previous trauma).

OA WITH CPPD

OA with CPPD commonly occurs at the knee, radiocarpal joint, second to third MCPJs, shoulder joint, and elbow joint. Patients with OA plus CPPD are usually older than [60] years.[64,65] More than a quarter of patients with knee OA who require hospital referral, and more than half of those undergoing total knee replacement for OA, have CPPD.[44,66] The presence of CPPD may modify OA symptoms,[44,67] presumably because CPP crystals are hard, negatively charged particles that can exert both proinflammatory and adverse mechanical effects.[68] Com

Key points

- Hand OA is usually bilaterally symmetric. Symptoms affect just 1 or a few joints at a time. Symptoms are often intermittent and occur at the target sites, namely DIPJs (w50%), thumb bases (w35%), PIPJs (w20%), and MCPJs (w10%), in descending order of frequency.
- Individuals without pain may report a dull ache or stiffness. The symptoms of hand OA deteriorate in half the patients over the next 6 years. The predictors of a worse clinical outcome include a high level of functional impairment at baseline and a greater number of painful joints, with no correlation between clinical change and radiographic progression.

Table 4
Common periarticular lesions near the hip

Soft Tissue Disorder	Signs and Symptoms
Trochanteric bursitis/gluteus medius tendinitis [a]	Lateral hip pain, worse on lying on that side at night and reproduced by pressure over the greater trochanter region
Iliopsoas bursitis	Anterior groin pain ± swelling. Frequently associates with other arthropathies
Ischiogluteal bursitis	Pain over the ischia, aggravated by local pressure brought on by sitting and lying. Local tenderness present
Adductor tendinitis	Medial groin pain aggravated by passive hip abduction and resisted active adduction

[a] Most common.

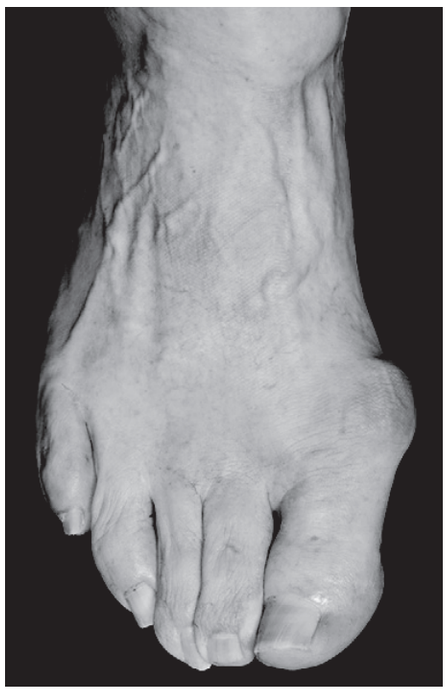


Fig. 10. First MTPJ OA with hallux valgus and an inflamed overlying superficial bursa ("bunion").

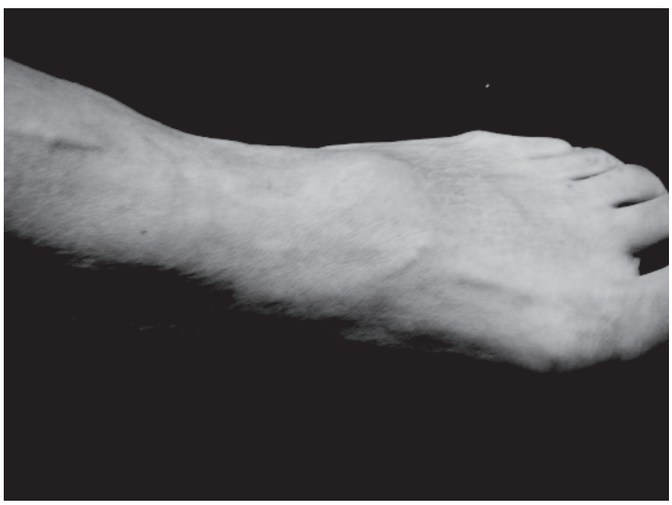


Fig. 11. Midfoot OA aggravated by pes planus. Note coexistent hallux valgus, suggesting first MTPJ OA.

pared with OA without CPPD, there may be a longer duration of early morning stiffness and more common and pronounced acute, intermittent, or low-grade and persistent synovitis (Fig. 12). Joint effusions are common, and may be hemorrhagic or turbid on aspiration. Large effusions, mainly at the knee or the shoulder, may leak into the surrounding soft tissues and lead to localized pain, swelling, and extensive bruising. Although studies give conflicting results, it is likely that OA with CPPD is not more rapidly progressive than OA alone.[66,69,70] However, there are anecdotal reports of patients with CPPD developing rapidly progressive destructive arthropathy at knees, shoulders, or hips. Some patients with OA with CPPD may have polyarticular arthropathy involving the knees, wrists, and the MCPJs that superficially mimics RA.

CLINICAL FEATURES INFLUENCE THE MANAGEMENT OF OA

Because OA has a diverse clinical present tion, it is important to target the therapeutic intervention to the patient, and to the symptoms. Patient education, appropriate advice concerning exercise and activity (ideally with physiotherapy and/or occupational therapy input), avoidance of adverse biomechanical factors, and adjunctive analgesia, are core to the management of OA. Oral paracetamol and topical analgesics (nonsteroidal antiinflamatory drugs, capsaicin) are recommended analgesics to try first, mainly based on their safety, but subsequent choice of analgesic depends on the clinical feature. For example, patients with pain and nonrestorative sleep may benefit from amitriptyline, nortriptyline, or duloxetine,[71] whereas patients with neuropathic features to their pain may benefit from duloxetine, pregabalin, or amitriptyline.[72] Some patients who

Key points

- Erosive OA is an aggressive subset of hand OA. It presents with subacute or insidious onset of pain, stiffness, soft tissue swelling, and sometimes paresthesia affecting multiple IPJs (synchronous polyarticular onset). Pain, tenderness, inflammation (warmth, soft tissue swelling, sometimes erythema) are more marked and prolonged compared with nodal hand OA and there is no association with GOA.

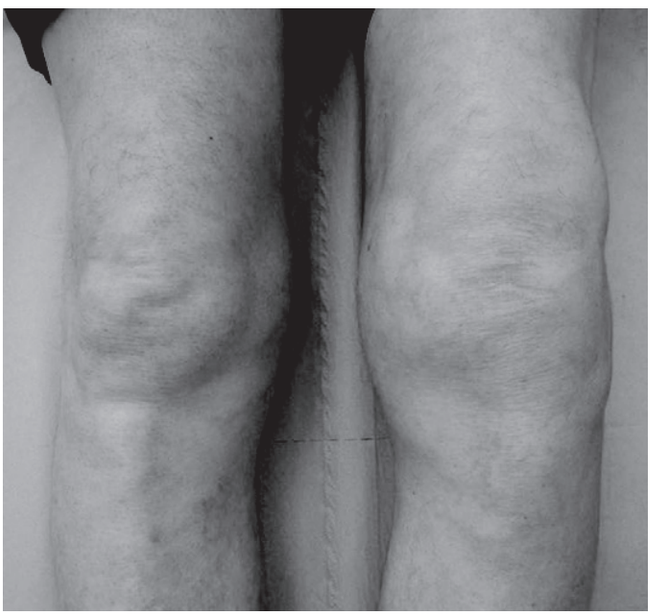


Fig. 12. Knee effusions are usually not marked in OA. This person with OA plus CPPD had a large left knee effusion expanding the suprapatellar pouch, giving a positive balloon sign (fluctuance) on palpation.

Key points

- The knee is an important target site for OA. Knee OA alone is the commonest cause of lower limb disability in elderly people. It is usually bilateral, although symptoms may be more pronounced on 1 side. Unilateral knee OA is more common in young men, and is often caused by prior knee injury or surgery. Most patients with knee OA have medial compartment tibiofemoral joint (TFJ) OA, PFJ OA, or a combination of both.

present with rapidly progressive severe OA of the knees or hips may warrant consideration for joint replacement surgery, whereas others who present with exacerbation of their joint symptoms may benefit from local intraarticular injections of corticosteroid to achieve short-term symptom control. The latter is especially true in those with thumb base, knee, and hip OA. Those with superadded acute CPP crystal arthritis may also derive rapid benefit from intra-articular corticosteroid injection and/or colchicine. In contrast, asymptomatic radiographic changes of OA in peripheral or spinal joints in the elderly require no further interventions apart from possibly modifying risk factors for the progression of OA (eg, obesity). The presence of comorbid fibromyalgia should be specifically sought and treated in patients who present with severe OA, and in those with symptomatic OA at several sites. Patients with GOA may have a worse prognosis than those without GOA, and should be targeted for risk factor modification (eg, patients with knee OA in the context of GOA are at higher risk of progression of their knee OA).[19]

SUMMARY

Usage-related pain, short-lived morning/i activity stiffness, and locomotor restriction are the most common symptoms of OA. In patients with typical presentation at the target sites, clinical assessment alone is sufficient to allow a diagnosis of OA. Patients with OA should be assessed in a holistic manner, which should include a targeted examination for the associated comorbidities.

■ References

1. Lane NE, Brandt K, Hawker G, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. Osteoarthritis Cartilage 2011;19(5):478–82.
2. National Institute for Health and Clinical Excellence. Osteoarthritis: the care and management of osteoarthritis in adults. [CG59]. London: Na tional Institute for Health and Clinical Excellence; 2008.
3. Abhishek A, Doherty M. Disease diagnosis and clinical presentation. In: Henrotin Y, Hunter DJ, Kawaguchi H, editors. OARSI Online Primer. OARSI; 2011.
4. Yusuf E, Kortekaas MC, Watt I, et al. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. Ann Rheum Dis 2011;70(1):60–7.
5. Goddard NJ, Gosling PT. Intra-articular fluid pressure and pain in osteo arthritis of the hip. J Bone Joint Surg Br 1988;70(1):52–5.
6. Hawker GA, Stewart L, French MR, et al. Understanding the pain expe rience in hip and knee osteoarthritis–an OARSI/OMERACT initiative. Os teoarthritis Cartilage 2008;16(4):415–22.
7. Allen KD, Coffman CJ, Golightly YM, et al. Daily pain variations among patients with hand, hip, and knee osteoarthritis. Osteoarthritis Cartilage 2009;17(10): 1275–82.
8. Hill CL, Gale DR, Chaisson CE, et al. Periarticular lesions detected on magnetic resonance imaging: prevalence in knees with and without symptoms. Arthritis Rheum 2003;48(10):2836–44.
9. Altman R, Asch E, Bloch D, et al. Development of criteria for the classifi cation and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the Ameri can Rheumatism Association. Arthritis Rheum 1986;29(8):1039–49.
10. Ike R, O'Rourke KS. Compartment-directed physical examination of the knee can predict articular cartilage abnormalities disclosed by needle arthroscopy. Arthritis Rheum 1995;38(7):917–25.
11. Sale JE, Gignac M, Hawker G. The relationship between disease symp toms, life events, coping and treatment, and depression among older adults with osteoarthritis. J Rheumatol 2008;35(2):335–42.
12. Abad VC, Sarinas PS, Guilleminault C. Sleep and rheumatologic disor ders. Sleep Med Rev 2008;12(3):211–28.
13. Imamura M, Imamura ST, Kaziyama HH, et al. Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis. Arthritis Rheum 2008;59(10):1424–31.
14. Edwards RR, Bingham CO 3rd, Bathon J, et al. Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. Arthritis Rheum 2006; 55(2):325–32.
15. Suri P, Morgenroth DC, Kwoh CK, et al. Low back pain and other mus culoskeletal pain comorbidities in individuals with symptomatic osteoar thritis of the knee: data from the osteoarthritis initiative. Arthritis Care Res (Hoboken) 2010;62(12): 1715–23.
16. Hurley MV, Scott DL, Rees J, et al. Sensorimotor changes and functional performance in patients with knee osteoarthritis. Ann Rheum Dis 1997;56(11):641–8.
17. Petrie KJ, Jago LA, Devcich DA. The role of illness perceptions in patients with medical conditions. Curr Opin Psychiatry 2007;20(2):163–7.
18. van Dijk GM, Dekker J, Veenhof C, et al. Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the liter ature. Arthritis Rheum 2006;55(5):779–85.
19. Chapple CM, Nicholson H, Baxter GD, et al. Patient characteristics that predict progression of knee osteoarthritis: a systematic review of prog nostic studies. Arthritis Care Res (Hoboken) 2011;63(8):1115–25.
20. Harvey WF, Yang M, Cooke TD, et al. Association of leg-length inequal ity with knee osteoarthritis: a cohort study. Ann Intern Med 2010;152(5):287–95.
21. Golightly YM, Allen KD, Helmick CG, et al. Hazard of incident and pro gressive knee and hip radiographic osteoarthritis and chronic joint symp toms in individuals with and without limb length inequality. J Rheumatol 2010;37(10): 2133–40.
22. Zhang W, Doherty M, Peat G, et al. EULAR evidence-based recommen dations for the diagnosis of knee osteoarthritis. Ann Rheum Dis 2010;69(3):483–9.
23. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence-based recommen dations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. Ann Rheum Dis 2009;68(1):8–17.
24. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskelet Disord 2008;9:116.
25. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthri tis of the hip. Arthritis Rheum 1991;34(5):505–14.
26. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthri tis of the hand. Arthritis Rheum 1990;33(11):1601–10.
27. Peat G, Thomas E, Duncan R, et al. Clinical classification criteria for knee osteoarthritis: performance in the general population and primary care. Ann Rheum Dis 2006;65(10):1363–7.
28. Thorstensson CA, Andersson ML, Jonsson H, et al. Natural course of knee osteoarthritis in middle-aged subjects with knee pain: 12-year fol low-up using clinical and radiographic criteria. Ann Rheum Dis 2009;68(12):1890–3.
29. Wolfe F, Lane NE. The longterm outcome of osteoarthritis: rates and predictors of joint space narrowing in symptomatic patients with knee osteoarthritis. J Rheumatol 2002;29(1):139–46.
30. Picavet HS, Hazes JM. Prevalence of self reported musculoskeletal dis eases is high. Ann Rheum Dis 2003;62(7):644–50.

31. Zhang W, Neame R, Doherty S, et al. Relative risk of knee chondrocalci nosis in siblings of index cases with pyrophosphate arthropathy. Ann Rheum Dis 2004; 63(8):969–73.
32. van Saase JL, van Romunde LK, Cats A, et al. Epidemiology of osteoar thritis: Zoetermeer survey. Comparison of radiological os teoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989;48(4):271–80.
33. Kellgren JH, Moore R. Generalized osteoarthritis and Heberden's nodes. Br Med J 1952;1(4751):181–7.
34. Kellgren JH, Lawrence JS, Bier F. Genetic factors in generalized osteo-ar throsis. Ann Rheum Dis 1963;22:237–55.
35. Lawrence JS. Generalized osteoarthrosis in a population sample. Am J Epidemiol 1969;90(5):381–9.
36. Dahaghin S, Bierma-Zeinstra SM, Ginai AZ, et al. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and dis ability (the Rotterdam Study). Ann Rheum Dis 2005;64(5):682–7.
37. Bijsterbosch J, Watt I, Meulenbelt I, et al. Clinical and radiographic dis ease course of hand osteoarthritis and determinants of outcome after 6 years. Ann Rheum Dis 2011;70(1):68–73.
38. Williams WV, Cope R, Gaunt WD, et al. Metacarpophalangeal arthrop athy associated with manual labor (Missouri metacarpal syndrome). Clinical radiographic, and pathologic characteristics of an unusual de generation process. Arthritis Rheum 1987;30(12):1362–71.
39. Punzi L, Ramonda R, Sfriso P. Erosive osteoarthritis. Best Pract Res Clin Rheumatol 2004;18(5):739–58.
40. Punzi L, Frigato M, Frallonardo P, et al. Inflammatory osteoarthritis of the hand. Best Pract Res Clin Rheumatol 2010;24(3):301–12.
41. Bijsterbosch J, Watt I, Meulenbelt I, et al. Clinical burden of erosive hand osteoarthritis and its relationship to nodes. Ann Rheum Dis 2010;69(10):1784–8.
42. Cavasin F, Punzi L, Ramonda R, et al. Prevalence of erosive osteoarthritis of the hand in a population from Venetian area. Reumatismo 2004;56(1):46–50 [in Italian].
43. Duncan RC, Hay EM, Saklatvala J, et al. Prevalence of radiographic os teoarthritis–it all depends on your point of view. Rheumatology (Oxford) 2006;45(6): 757–60.
44. Ledingham J, Regan M, Jones A, et al. Radiographic patterns and asso ciations of osteoarthritis of the knee in patients referred to hospital. Ann Rheum Dis 1993; 52(7):520–6.
45. Creamer P, Lethbridge-Cejku M, Hochberg MC. Where does it hurt? Pain localization in osteoarthritis of the knee. Osteoarthritis Cartilage 1998;6(5):318–23.
46. Wood LR, Peat G, Thomas E, et al. Knee osteoarthritis in communi ty-dwelling older adults: are there characteristic patterns of pain loca tion? Osteoarthritis Cartilage 2007;15(6):615–23.
47. Slemenda C, Brandt KD, Heilman DK, et al. Quadriceps weakness and osteoarthritis of the knee. Ann Intern Med 1997;127(2):97–104.
48. Hinman RS, Hunt MA, Creaby MW, et al. Hip muscle weakness in indi viduals with medial knee osteoarthritis. Arthritis Care Res (Hoboken) 2010;62(8):1190–3.
49. Cibere J, Zhang H, Thorne A, et al. Association of clinical findings with preradiographic and radiographic knee osteoarthritis in a population-based study. Arthritis Care Res (Hoboken) 2010;62(12):1691–8.
50. O'Reilly S, Doherty M. Signs, symptoms, and laboratory tests. In: Brandt KD, Doherty M, Lohmander LS, editors. Osteoarthritis. Oxford (England): Oxford; 2003. p. 197–210.
51. Rothstein CP, Laorr A, Helms CA, et al. Semimembranosus-tibial collat eralligament bursitis: MR imaging findings. AJR Am J Roent genol 1996;166(4): 875–7.
52. Crawford RW, Gie GA, Ling RS, et al. Diagnostic value of intra-articular anaesthetic in primary osteoarthritis of the hip. J Bone Joint Surg Br 1998;80(2):279–81.
53. Gofton JP. Studies in osteoarthritis of the hip. I. Classification. Can Med Assoc J 1971;104(8):679–83.
54. Ledingham J, Dawson S, Preston B, et al. Radiographic patterns and associations of osteoarthritis of the hip. Ann Rheum Dis 1992;51(10):1111–6.
55. Lanyon P, Muir K, Doherty S, et al. Influence of radiographic phenotype on risk of hip osteoarthritis within families. Ann Rheum Dis 2004;63(3):259–63.
56. Della Torre P, Picuti G, Di Filippo P. Rapidly progressive osteoarthritis of the hip. Ital J Orthop Traumatol 1987;13(2):187–200.
57. Dieppe PA, Crocker P, Huskisson EC, et al. Apatite deposition disease. A new arthropathy. Lancet 1976;1(7954):266–9.
58. Dieppe PA, Doherty M, Macfarlane DG, et al. Apatite associated destruc tive arthritis. Br J Rheumatol 1984;23(2):84–91.
59. Nuki G. Apatite associated arthritis. Br J Rheumatol 1984;23(2):81–3.
60. McCarty DJ, Halverson PB, Carrera GF, et al. "Milwaukee shoulder"–as sociation of microspheroids containing hydroxyapatite crystals, active collagenase, and neutral protease with rotator cuff defects. I. Clinical aspects. Arthritis Rheum 1981;24(3):464–73.
61. Williams BS, Cohen SP. Greater trochanteric pain syndrome: a review of anatomy,diagnosis and treatment. Anesth Analg 2009;108(5):1662–70.
62. Kalichman L, Hunter DJ. Lumbar facet joint osteoarthritis: a review. Se min Arthritis Rheum 2007;37(2):69–80.
63. van Eerd M, Patijn J, Lataster A, et al. 5. Cervical facet pain. Pain Pract 2010; 10(2):113–23.
64. Dieppe PA, Alexander GJ, Jones HE, et al. Pyrophosphate arthropathy: a clinical and radiological study of 105 cases. Ann Rheum Dis 1982;41(4):371–6.
65. Felson DT, Anderson JJ, Naimark A, et al. The prevalence of chondrocal cinosis in the elderly and its association with knee osteoarthritis: the Framingham Study. J Rheumatol 1989;16(9):1241–5.
66. Viriyavejkul P, Wilairatana V, Tanavalee A, et characteristics of patients with and without calcium pyrophosphate dihydrate crystal deposition disease who underwent total knee replacement surgery for osteoarthritis. Osteoarthritis Cartilage 2007;15(2):232–5.
67. Pattrick M, Hamilton E, Wilson R, et al. Association of radiographic changes of osteoarthritis, symptoms, and synovial fluid particles in 300 knees. Ann Rheum Dis 1993;52(2):97–103.
68. Liu YZ, Jackson AP, Cosgrove SD. Contribution of calcium-containing crystals to cartilage degradation and synovial inflammation in osteoar thritis. Osteoarthritis Cartilage 2009;17(10):1333–40.
69. Ledingham J, Regan M, Jones A, et al. Factors affecting radiographic progression of knee osteoarthritis. Ann Rheum Dis 1995;54(1):53–8.
70. Neogi T, Nevitt M, Niu J, et al. Lack of association between chondrocal cinosis and increased risk of cartilage loss in knees with osteoarthritis: results of two prospective longitudinal magnetic resonance imaging studies. Arthritis Rheum 2006;54(6):1822–8.
71. Carville SF, Arendt-Nielsen S, Bliddal H, et al. EULAR evidence-based rec ommendations for the management of fibromyalgia syndrome. Ann Rheum Dis 2008;67(4):536–41.
72. National Institute for Health and Clinical Excellence. Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings. [CG96]. London: National Institute for Health and Clinical Excellence; 2010.

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Diagnosis and treatment of hip and knee osteoarthritis: A review

ABSTRACT :

Importance: Osteoarthritis (OA) affects more than 240 million people worldwide and is the most frequent reason for activity limitation in adults. This review focuses on hip and knee OA.

Observations: OA is the most common type of arthritis. It can involve almost any joint but typically affects the hands, knees, hips and feet. It is characterized by pathologic changes in cartilage, bone, synovium, ligament, muscle, and periarticular fat, leading to joint dysfunction, pain, stiffness, functional limitation, and loss of valued activities. Risk factors include age, female sex, obesity, genetics and major joint injury. Persons with OA have more comorbidities and are more sedentary than those without OA. The reduced physical activity leads to a 20% higher age- adjusted mortality. Several physical examination findings are useful diagnostically, including bony enlargement in knee OA and pain elicited with internal hip rotation in hip OA. Radiographic indicators include marginal osteophytes and joint space narrowing. The cornerstones of OA management are prescribed exercises, weight loss if appropriate, and education—complemented by topical or oral NSAIDs, in those without contraindications. Intraarticular steroid injections provide short-term pain relief and duloxetine has demonstrated efficacy. Opiates should be avoided. Clinical trials have shown promising results for compounds that arrest structural progression (e.g. cathepsin K inhibitors, Wnt inhibitors, anabolic growth factors), or reduce OA pain (e.g. nerve growth factor inhibitors). Persons with advanced symptoms and structural damage are candidates for total joint replacement. Racial and ethnic disparities persist in the utilization and outcomes of joint replacement.

Conclusions and Relevance: Hip and knee OA are highly prevalent and disabling. Education, exercise and weight loss are cornerstones of management, complemented by NSAIDS (in those who are candidates), corticosteroid injections, and several adjunctive medications. In persons with advanced symptoms and structural damage, total joint replacement effectively relieves pain.

1. INTRODUCTION

Long characterized as a 'wear and tear' disorder, osteoarthritis (OA) is now understood to have a complex pathophysiology affecting multiple joints and joint structures, as captured by the Osteoarthritis Research Society International definition of OA: "The disease manifests first as a molecular derangement (abno mal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness."[1]

Worldwide, an estimated 240 million persons have symptomatic, activity-limiting OA.[2,3] The knee and hip are two commonly affected joints and are the focus of this review. Nearly 30% of individuals greater than 45 years old have radiographic evidence of knee OA, about half of whom have knee symptoms.[4,5] The prevalence of symptomatic, radiographic hip OA is around 10%.[6,7]

The lifetime risk of symptomatic knee OA is greater in obese persons (BMI ≥ 30 kg/m2) than nonobese persons (19.7% versus 10.9%).[8] Prior joint trauma, such as anterior cruciate ligament rupture and ankle fracture, increases risk, accounting for 12% of knee OA cases.[9] The prevalence of symptomatic, radiographic knee OA was 11.4% in women and 6.8% in men in one large cohort study[4] and 18.7% in women and 13.5% in men in another large cohort study.[5] As compared to males with OA, women have more severe radiographic findings and symptoms.[10] Older age and female sex are risk factors for hip OA as well as knee OA. In addition, congenital and acquired anatomic abnormalities (e.g. hip dysplasia) are risk factors for hip OA. Regarding race, African Americans and whites have similar prevalence of hip OA (accounting for race, sex and body mass index), while African Americans, especially women, have higher prevalence of knee OA.[5,7]

OA leads to substantial cost and mortality. Forty-three percent of the 54 million individuals in the US living with arthritis (most of whom have OA) experience arthritis-related limitations in daily activities.[11] Wage losses due to OA amount to $65 billion and direct medical costs exceed $100 billion.[2,12] Persons with knee OA spend, on average, around $15,000 dollars (discounted) over their lifetimes on direct medical costs of OA.[13] OA is commonly associated with comorbidities, which may stem from lack of physical activity, medication toxicity, and the effects of inflammatory cytokines. It has been estimated that 31% of persons with OA have ≥5 comorbid conditions.[2] Persons with hip and knee OA have ~20% excess mortality as compared with age-matched controls, due in part to lower levels of physical activity.[2]

Methods

We searched PubMed for English-language articles on the dia nosis and management of hip and knee OA, using the search terms osteoarthritis and treatment; osteoarthritis and epidemiology; osteoarthritis and diagnosis or imaging; osteoarthritis and disability or comorbidity. We reviewed these publications and relevant references in these papers. We based our conclusions

on treatment efficacy primarily using the rigorous systematic literature syntheses and metaanalyses that support the Osteoarthritis Re tudies is the standardized mean difference (SMD), the mean difference in improvement between active treatment and placebo, divided by the standard deviation of the difference. For questions not addressed by the metaanalyses, we provide results of pivotal trials.

Pathophysiology

OA arises from complex biological processes that include cartilage, bone, synovium, ligaments, periarticular fat, meniscus, and muscle.[15] The classic features of OA noted on radiographs include joint space narrowing due to loss of articular cartilage and meniscus, and bony changes including sclerosis of subchondral bone and osteophytes (Figure 1A). The effects of OA on cartilage, meniscus, syovium, subchondral bone and other structures can be appreciated on magnetic resonance imaging (Figure 1B).

The biomechanical environment influences the disease process. Varus alignment of the lower extremities ("bowlegged") shifts load medially, increasing risk of medial compartment knee OA, while valgus alignment ("knocked knees") shifts load laterally leading to lateral compartment OA. These abnormalities in alignment are risk factors for OA incidence and, more importantly, for OA progression.[16,17] Excessive loading of bone may result in bone marrow lesions, seen on magnetic resonance imaging (Figure 1B).[18] Histologically, bone marrow lesions contain microfractures with bone fragments, necrosis, fibrosis and abnormal adipocytes suggestive of focal areas of damage and remodeling due to abnormal loading.[19]

Synovitis is commonly noted in OA joints.[20] The synovitis seen in OA has a predominance of macrophages while the synovitis of rheumatoid arthritis (RA) has a predominance of T cells.[21] This reflects activation of the innate immune response in OA joints, likely due to damage of joint tissues resulting in a chronic wound type of environment.[22] OA synovitis is more focal than in RA; in the knee, it is commonly found in the suprapatellar pouch.[23] Synovitis plays a prominent role in joint destruction in RA, while its role in the progression of OA may be limited to a subset of individuals.

Many proinflammatory cytokines and growth factors have been identified in the OA joint (Figure 2.) Cytokines present at relatively high levels in OA synovial fluid include IL-6, MCP-1, VEGF, IP-10 and MIG.24 The pro-inflammatory factors are responsible for the progressive destruction and remodeling of the joint through the stimulation of matrix- degrading enzymes, including the matrix metalloproteinases.[15,25] The growth factors that normally would stimulate matrix production and repair of joint tissues are overwhelmed by pro-inflammatory mediators. Certain growth factors including TGF□ and BMP-2 promote osteophyte formation and contribute to subchondral sclerosis. The pro-inflammatory mediators and anabolic factors are produced locally by the cells within the affected tissues including the articular chondrocytes, synovial fibroblasts and immune cells in the synovium, inflammatory cells in periarticular fat, as well as cells in bone, including osteoblasts, osteocytes, osteoclasts and bone marrow mesenchymal stem cells (Figure 3).[15,26] The cytokines are potential targets for disease modification in OA; however, currently it is not clear which cytokines are primary drivers of joint destruction, and which are involved secondarily.

Clinical presentation

Patients with OA typically present with pain and stiffness in the affected joint(s). Stiffness is worse in the morning or on arising after prolonged sitting, and improves within 30 minutes. Pain is use-related early in the course, but can become less predictable over time. While sometimes viewed as a disease of inexorable worsening, natural history studies show that most patients report little change in symptoms over six years of observation.[27]

Assessment and Diagnosis

The clinician must distinguish symptomatic OA from other entities that can cause hip or knee pain, including inflammatory (e.g. rheumatoid and psoriatic) arthritis, infectious and crystalline (e.g. gout, pseudogout) arthritis and soft tissue lesions such as bursitis, tendonitis, and meniscal tear. The stiffness in inflammatory arthritis may last over an hour. The pain of infectious arthritis and crystalline arthritis is typically acute. Individuals with retropatellar pain may have patellofemoral OA, which can exist in isolation or in the presence of tibiofemoral OA. Because the patellofemoral joint is loaded when the knee is bent, patellofemoral OA is especially painful when

Key points

- The differential diagnosis for hand OA is wide, and includes:
- Psoriatic arthritis: targets DIPJs or affects just 1 ray
- RA: targets wrists, MCPJs, PIPJs
- Gout: may be superimposed on preexisting hand OA
- Hemochromatosis: mainly targets MCPJs, and wrists

Key points

- Hip OA presents with pain, stiffness, and rstricted movement. Pain caused by hip OA is usually maximal deep in the anterior groin, but may spread to the anteromedial or upper lateral thigh, and occasionally the buttocks. Distal radiation is common, and pain may predominate at the knee. Some people present with knee pain without any proximal pain; unlike knee-originated pain, such hip referred pain is usually more generalized, involves the distal thigh, and may be improved by rubbing. Pain in hip OA is exacerbated by rising from a seated position, and during initial or midambulation.

patients ascend and descend stairs and get in and out of cars or a bath.28 The syndrome of patellofemoral pain is common and often arises from malalignment of the patella in the femoral groove (due for example to asymmetric tension from the lateral and medial quadriceps) rather than from OA.

On physical exam, knee effusions are generally either absent or small and cool in persons with OA. Those with effusions may have popliteal or "Bakers" cysts, which are extensions of the synovial swelling that can be palpated in the posterior aspect of the knee. In contrast, the knee often has warm, easily palpable effusions in inflammatory, infectious and crystalline arthritis. Soft tissue lesions such as anserine bursitis and trochanteric bursitis are extra-articular and do not cause joint effusions; they are identified by local tenderness. Effusions cannot be detected on physical exam of recessed joints such as the hip. Infectious, crystalline and other inflammatory arthritides can be distinguished incisively from OA because the synovial fluid white blood cells exceed 2000 cells/cc in these disorders.

The sensitivities, specificities and likelihood ratios of various elements of the physical examination and radiographic features for hip and knee OA are shown in Table 1. Bony enlargement on physical examination is specific (95%) for knee OA, though somewhat insensitive (55%), while crepitus is sensitive (89%) though somewhat nonspecific (58%).[29] Osteophytes on knee radiographs are both sensitive (91%) and fairly specific (83%). The combination of osteophytes AND knee pain has good sensitivity (83%) and specificity (93%), with likelihood ratio of 11.9.29 (The likelihood ratio = sensitivity / (1 – specificity). If the likelihood ratio is > 1, a positive test indicates that the post-test probability of disease is greater than the pre-test probability.

A recent review provided detailed data on the utility of physical examination maneuvers in the diagnosis of hip OA, and a video demonstration of the hip examination.[30,31] Hip internal rotation <15 degrees is moderately sensitive (66%) and specific (72%), as is limited hip adduction (80% sensitive, 81% specific).[30,32] Pain with hip internal rotation is more sensitive (82%) but less specific (39%). Osteophytes on radiographs are both sensitive (89%) and specific (90%). The combination of hip pain PLUS an osteophyte is also quite sensitive (89%) and specific (90%).[32]

These data suggest a presumptive diagnosis of hip or knee OA can be made on the basis of the history and physical exam. Radiographs portray the severity of structural damage and improve specificity when osteophytes or joint space narrowing are present. Pathologic features and symptoms of OA can occur before osteophytes are present on radiographs. Thus, a normal radiograph does not exclude OA. If the clinical presentation is highly suggestive of OA, clinicians should initiate management (detailed below) despite normal radiographs. Knee radiographs should be performed with the patient standing to reveal the extent of joint space narrowing of the tibiofemoral joint. For research purposes, hip and knee radiographs are typically assessed with the Kellgren-Lawrence grading system, with grade 0 representing no pathologic findings; Grade 1 questionable osteophytes; Grade 2 definite osteophytes; Grade 3, definite joint space narrowing; and Grade 4 advanced joint space narrowing.[33,34] The radiograph in Figure 1A is Kellgren-Lawrence Grade 3 and nearly K-L 4 because of the advanced medial joint space narrowing is nearly bone-on-bone.

Hip radiographs typically include an anteroposterior view and a lateral view. Weight-bearing is not necessary. The inter- and intra-rater reliabilities of hip radiographs for detecting joint space narrowing are high.[35] Hip radiographs involve greater exposure to ionizing radiation than radiographs of the chest or knee.

MRI is seldom indicated in the assessment or management of knee or hip OA. MRI detects changes in cartilage, meniscus (knee), labrum (hip), bone and synovium, providing a fuller picture of pathological involvement (Figure 1B).[36] Because of its high sensitivity[36], MRI is useful for research studies to identify early OA and document structural changes over time. In clinical care, MRI can be useful if there is suspicion of conditions such as subchondral insufficiency fracture, tumor or infection that would be treated differently and more urgently than OA.

Ultrasound can visualize joint effusion, osteophytes and other features.[37] As compared with MRI, ultrasound has sensitivity and specificity exceeding 85% for detecting osteophytes.Ultrasound is not as accurate as MRI in assessing joint space narrowing.[38] Because ultrasound is less expensive and more portable than MRI, it is used frequently in Europe and a growing number of US centers in the diagnosis of OA and assessment of progression.

Treatment

Several professional organizations have developed guidelines for OA management (Table 2). The guidelines suggest that patients with OA should be offered a core set of non-pharmacological interventions including education, weight loss (for those who are overweight), and exercises (strengthening, cardiovascular, and/or mind-body exercises such as Yoga or Tai Chi).[14,39–44]

Structured exercise interventions that typically focus on strengthening of lower extremity muscles offer improvements in pain and functional status (SMD of 0.52 for knee OA and 0.34 for hip OA; Table 3). A randomized controlled trial of a structured walking program showed a reduction in pain scores of 1.38 points (on a 0-10 scale) in the walking group and just 0.1 points in the control group (p=0.003).[45] Referral to a physical therapist is appropriate to initiate such a program, or to address lower extremity weakness or limitations in hip or knee range of motion. A combination of diet and exercise can result in substantial weight loss, pain relief, improvement in functional status, and reduction in inflammatory markers, as compared with exercise alone.[46]

While trials of lateral wedge shoe inserts have not been efficacious, a recent trial of an individualized external orthotic (attached below the sole) was associated with greater improvement in pain and functional status than a control orthotic.[47] This observation should be replicated before being advanced to routine use.

Non-steroidal anti-inflammatory drugs (NSAIDs) are first line pharmacologic treatment for OA. In numerous placebo-controlled trials, NSAIDs have resulted in greater pain relief than placebo, with standardized mean differences in pain and function scores of ~ 0.33 standard deviations, reflecting a moderate effect (Table 3). Many NSAIDs are available over the counter. Topical NSAIDs generally have less gastrointestinal toxicity than oral NSAIDs,[14,44] but are less useful in hip OA because the joint is recessed.

NSAIDs have important toxicities, including gastrointestinal irritation and ulceration, bleeding, and decreased renal blood flow with azotemia. Patients on anticoagulants who wish to take an NSAID should use a COX-2 inhibitor (such as celecoxib), which does not increase bleeding. Those with dyspepsia should use proton pump inhibitors and/or a COX-2 inhibitor. Patients with history of bleeding peptic ulcer are typically not prescribed NSAIDs at all. Risk factors for gastrointestinal bleeding from NSAIDs include older age, medical comorbidities, and concomitant use of corticosteroids and anticoagulants.[48] Individuals with cardiovascular or renal disease are at risk of renal toxicity; alternatives to NSAIDs should be discussed. Acetaminophen is less efficacious than NSAIDs in management of knee (SMD 0.05) and hip (SMD 0.23) OA.[49–53] It is a reasonable, safe alternative for those intolerant to NSAIDs but should not be used in persons with liver disease or risk factors such as heavy alcohol use. The Medical Letter table published in this issue of JAMA provides rich information on formulations, dosages and costs of many of the pharmacologic agents noted in this review.

Patients unable to take NSAIDs, or who do not respond, can try intra-articular corticosteroid injections, which typically relieve pain for a few weeks.[54] They are especially helpful in patients with OA of a single joint that can be injected easily, such as the knee. The hip is generally injected under imaging (fluoroscopy or ultrasound) guidance. Corticosteroid injections have no greater effect on pain than placebo after three months,[55] and may be inferior to physical therapy at one year.[56] A newer formulation of steroid injection (triamcinolone acetonide extended release) appears to have fewer systemic effects than traditional steroid injections.[57] Some studies have suggested that intraarticular steroid injections may have deleterious effects on cartilage[55,58]; the clinical meaning of these findings is not yet known.

Injection of intra-articular hyaluronic acid (HA) products is another option for patients

Key points

- Symptoms are worse in the morning and during periods of inactivity, and are increased:
- Stress
- Exercise
- Lumbar spine extension
- Rotary motions
- Standing
- Sitting

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with persistent pain despite NSAIDs. Guidelines differ regarding recommendations of intraarticular HA (Table 2).[14,40–44] While efficacy of HA injections is similar to that of NSAIDs (SMD 0.37, Table 3), the highest quality trials showed weaker effects. Injection of growth factors, such as those found in platelet-rich plasma, and injection of stem cell preparations, are increasing in use. However, these products are non-standardized and studies of these agents are weak.

Osteoarthritis pain may be mediated in part by mechanisms in the central nervous system. Several medications have been used to address pain of central origin. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, has been shown in randomized trials to result in greater pain relief than placebo in persons with knee OA (SMD 0.39).[59,60] Gabapentin may have efficacy in knee OA, but evidence is limited.[61] Opiate analgesics are used by over 20% of patients with OA, but have limited efficacy for hip and knee OA (SMD ~0.20) and considerable toxicity including constipation, falls, somnolence, respiratory depression and potential for addiction. OA treatment guidelines advise against use of stronger opiates, with conditional recommendation of tramadol, a synthetic opioid agonist that also inhibits reuptake of serotonin and norepinephrine.[44]

To date, trials of biologics to inhibit IL-1 or TNFα in knee OA failed to relieve symptoms or halt structural progression, as compared with placebo.[62–64] However, a secondary analysis of the CANTOS trial (canakinumab anti-inflammatory thrombosis outcome study) demonstrated a significant reduction in the incidence of hip and knee replacement in those receiving anti-IL-1β, with a pooled HR of 0.58 (CI 0.42-0.80, p=0.001).[65] Some areas of current investigation for disease modification that are being examined in early phase studies include Wnt inhibiton[66], intra-articular injection of an anabolic growth factor FGF-1867 and a cathepsin K inhibitor.[68]

Patients with persistent pain and functional loss and advanced radiographic changes are candidates for total knee or hip replacement (TKR, THR). More than 700,000 primary TKRs and 330,000 primary THRs are done annually in the US, >90% for OA.[69] Ninety-day mortality is <1%, and serious complications at 90 days occur in <5%.[70–73] About 90% of recipients of THR and 80% of recipients of TKR report little to no residual pain following recovery from these procedures.[74] A randomized controlled trial of TKR vs. a rigorous physical therapy program showed that those receiving TKR improved in KOOS Pain score by 35 points (on a 0-100 scale), as compared with 17 points in those receiving PT (difference of 17 points (95% CI 10.4, 23.8).[75] Fewer than 10% of TKRs and ~20% of THRs need to be revised over 20 years.[76,77] The failure rate is higher in younger and more active recipients, those with comorbidities and those operated upon in low volume centers or by low volume surgeons.[78,79] The generally low revision rates mean that persons who receive TKR or THR in their 70's's are much more likely to die with their original implants in place than to need revision.[80] In the patient with unicompartmental knee OA, surgical options include unicondylar knee replacement and osteotomy as well as TKR. Arthroscopic debridement is not appropriate for treating OA; arthroscopic partical meniscectomy has a limited role in patients with OA and symptomatic meniscal tear, for whom nonoperative therapy was not helpful.[81–83]

Blacks and Hispanics are ~25% less likely to receive TKR than non-Hispanic whites, even after accounting for age and socioeconomic status.[72,84] These patterns are seen for THR as well.[85,86] Proposed reasons for these disparities in utilization include less frequent offers of joint replacement to non-Whites,[87] less willingness to undergo TJR, implicit bias, and other factors[88,89] Blacks and Hispanics also have higher risk of adverse outcomes including mortality after THR and joint infections following TKR.[90]

Several innovative interventions for OA have been introduced into clinical use but have not been evaluated with sufficient rigor to be recommended. The include geniculate artery embolization, water-cooled radiofrequency ablation and botox injections.

Evolving concepts in management of OA

OA consists of multiple phenotypes.[91] Knee OA developing after anterior cruciate ligamenttear might have a mechanism distinct from OA associated with obesity. Individuals mayhave more than one mechanism at play, requiring multi-modal management. It will beimportant to determine which individuals with early OA are more likely to progress

rapidly and would benefit from an intervention designed to slow disease progression. Machine learning approaches using datasets that include demographic, imaging and biomarker data are being harnessed to identify such subsets.[92]

Intensive research has identified potential targets for structure-modifying therapies,[66–68] including inhibitors of collagenases and aggrecanases that degrade cartilage, and of the cytokines and chemokines that contribute to the pro-inflammatory environment.[93] Pre- clinical evidence suggests that senescent cells in the joint contribute to OA by releasing pro- inflammatory mediators and matrix-degrading enzymes. Targeting these cells with senolytics that selectively kill senescent cells could be of value.[94] It remains unclear whether arresting progression of structural damage in OA will ultimately result in reduced pain and functional limitation.

In addition to structure modification, research in OA therapeutics has also focused on nerve growth factor (NGF), with several trials showing efficacy in pain relief with injections of anti-NGF antibodies.[95–97] However, individuals who received anti-NGF were more likely than those receiving placebo to experience rapid progression of OA requiring joint arthroplasty, especially if they were also taking NSAIDs. [98] If anti-NGF therapy is approved for OA, providers and patients will need to discuss risks and benefits carefully.

Prognosis

While some patients with OA follow a trajectory of steady increase in symptoms, others have waxing and waning pain over many years. There is also variability in the progression of joint damage. Model projections suggest that over 50% of persons in the US with symptomatic knee OA undergo TKR over their lifetimes.[13] Several factors influence the rapidity of radiographic and clinical progression including older age, reduced physical activity, the extent of cartilage damage, short term changes of cartilage damage, malalignment and more severe pain.[27,99,100]

Conclusion

Evolving insights into pathophysiology portend a new age in OA therapeutics, with therapies that can curb structural progression and provide more potent and/or safer pain relief. The efficacy of diet and exercise interventions suggests that breakthroughs in efforts to sustain weight loss could move the field forward. Taken together these advances may change the outlook for patients with this painful, costly, disabling condition.

Key points

- OA with CPPD commonly occurs at the knee, radiocarpal joint, second to third MCPJs, shoulder joint, and elbow joint. Patients with OA plus CPPD are usually older than 60 years. More than a quarter of patients with knee OA who require hospital referral, and more than half of those undergoing total knee replacement for OA, have CPPD.

■ References

1. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. Osteoarthritis Cartilage. 2015;23(8):1233–1241. [PubMed: 25865392]
2. Hawker G Osteoarthritis: a serious disease Osteoarthris Research Society International 2016. https:// www.oarsi.org/research/oa-serious-disease.
3. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet (London, England). 2015;386(9995):743–800.
4. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum. 1987;30(8):914–918. [PubMed: 3632732]
5. Jordan JM, Helmick CG, Renner JB, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. The Journal of Rheumatology. 2007;34(1):172. [PubMed: 17216685]
6. Haugen IK, Englund M, Aliabadi P, et al. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham Osteoarthritis Study. Ann Rheum Dis. 2011;70(9):1581–1586. [PubMed: 21622766]
7. Jordan JM, Helmick CG, Renner JB, et al. Prevalence of hip symptoms and radiographic and symptomatic hip osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. The Journal of rheumatology. 2009;36(4):809–815. [PubMed: 19286855]
8. Losina E, Weinstein AM, Reichmann WM, et al. Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. Arthritis Care Res (Hoboken). 2013;65(5):703–711. [PubMed: 23203864]
9. Brown TD, Johnston RC, Saltzman CL, Marsh JL, Buckwalter JA. Post traumatic osteoarthritis: a first estimate of incidence, prevalence, and burden of disease. Journal of orthopaedic trauma. 2006;20(10):739–744. [PubMed: 17106388]
10. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis Cartilage. 2005;13(9):769–781. [PubMed: 15978850]
11. Barbour KE, Helmick CG, Boring M, Brady TJ. Vital Signs: Prevalence of Doctor-DiagnosedArthritis and Arthritis-Attributable Activity - United States, 2013-2015. MMWR Morbidity and mortality weekly report. 2017;66(9):246–253. [PubMed: 28278145]
12. CPI for All Urban Consumers: All items in U.S. city average, all urban consumers, not seasonally adjusted 2019. https://data.bls.gov/pdq/SurveyOutputServlet. Accessed 1 April 2020.
13. Losina E, Paltiel AD, Weinstein AM, et al. Lifetime medical costs of knee osteoarthritis management in the United States: impact of extending indications for total knee arthroplasty. Arthritis care & research. 2015;67(2):203–215. [PubMed: 25048053]
14. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019;27(11):1578–1589. [PubMed: 31278997]
15. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: A disease of the joint as an organ. Arthritis Rheum. 2012;64:1697–1707. [PubMed: 22392533]
16. Brouwer GM, van Tol AW, Bergink AP, et al. Association between valgus

and varus alignment and the development and progression of radio graphic osteoarthritis of the knee. Arthritis Rheum. 2007;56(4):1204–1211. [PubMed: 17393449]
17. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA. 2001;286(2):188–195. [PubMed: 11448282]
18. Felson DT, McLaughlin S, Goggins J, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med. 2003;139(5 Pt 1):330–336. [PubMed: 12965941]
19. Taljanovic MS, Graham AR, Benjamin JB, et al. Bone marrow edema pattern in advanced hip osteoarthritis: quantitative assessment with magnetic resonance imaging and correlation with clinical examination, radiographic findings, and histopathology. Skeletal radiology. 2008;37(5):423–431. [PubMed: 18274742]
20. Felson DT, Niu J, Neogi T, et al. Synovitis and the risk of knee osteoar thritis: the MOST Study. Osteoarthritis Cartilage. 2016;24:458–464. [PubMed: 26432512]
21. Wood MJ, Leckenby A, Reynolds G, et al. Macrophage proliferation di tinguishes 2 subgroups of knee osteoarthritis patients. JCI insight 2019;4(2):e125325.
22. Orlowsky EW, Kraus VB. The Role of Innate Immunity in Osteoarthritis: When Our First Line of Defense Goes On the Offensive. The Journal of rheumatology. 2015; 42(3):363–371. [PubMed: 25593231]
23. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis patho genesis. Bone. 2012;51(2):249–257. [PubMed: 22387238]
24. Sohn DH, Sokolove J, Sharpe O, et al. Plasma proteins present in osteo arthritic synovial fluid can stimulate cytokine production via Toll-like re ceptor 4. Arthritis research & therapy. 2012;14(1):R7–R7. [PubMed: 22225630]
25. van den Bosch MHJ, van Lent P, van der Kraan PM. Identifying effector molecules, cells, and cytokines of innate immunity in OA. Osteoarthritis Cartilage. 2020;28(5):532–543. [PubMed: 32044352]
26. Lieberthal J, Sambamurthy N, Scanzello CR. Inflammation in joint injury and post-traumatic osteoarthritis. Osteoarthritis Cartilage. 2015;23(11):1825–1834. [PubMed: 26521728]
27. Collins JE, Katz JN, Dervan EE, Losina E. Trajectories and risk profiles of pain in persons with radiographic, symptomatic knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthritis Cartilage. 2014;22(5):622–630. [PubMed: 24662734]
28. Duncan R, Peat G, Thomas E, Wood L, Hay E, Croft P. Does isolated patellofemoral osteoarthritis matter? Osteoarthritis Carti lage. 2009;17(9):1151–1155. [PubMed: 19401244]
29. Altman R, Asch E, Bloch D, et al. Development of criteria for the classifi cation and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the Ameri can Rheumatism Association. Arthritis Rheum. 1986;29(8):1039–1049. [PubMed: 3741515]
30. Metcalfe D, Perry DC, Claireaux HA, Simel DL, Zogg CK, Costa ML. Does This Patient Have Hip Osteoarthritis?: The Rational Clinical Examination Systematic Review. JAMA. 2019;322(23):2323–2333. [PubMed: 31846019]
31. Does This Patient Have Hip Osteoarthritis: How to Provide a Hip Exam ination for Hip Osteoarthritis [Video]: JAMA Network 2019.
32. Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthri tis of the hip. Arthritis & Rheumatism. 1991;34(5):505– 514. [PubMed: 2025304]
33. Kohn MD, Sassoon AA, Fernando ND. Classifications in Brief: Kell gren-Lawrence Classification of Osteoarthritis. Clin Orthop Relat Res. 2 016;474(8):1886–1893. [PubMed: 26872913]
34. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16(4):494–502. [PubMed: 13498604]
35. Gold GE, Cicuttini F, Crema MD, et al. OARSI Clinical Trials Recommen dations: Hip imaging in clinical trials in osteoarthritis. Osteoarthritis Car tilage. 2015;23(5):716–731. [PubMed: 25952344]
36 . Hunter DJ, Zhang W, Conaghan PG, et al. Systematic review of the con current and predictive validity of MRI biomarkers in OA. Osteoarthritis Cartilage. 2011;19(5):557–588. [PubMed: 21396463]
37. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet (London, England). 2011;377(9783):2115–2126.
38. Podlipská J, Guermazi A, Lehenkari P, et al. Comparison of Diagnostic Performance of Semi- Quantitative Knee Ultrasound and Knee Radiog raphy with MRI: Oulu Knee Osteoarthritis Study.Scientific Reports. 2016;6:22365. [PubMed: 26926836]
39. Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non- pharmacological core management of hip and knee osteoar thritis. Ann Rheum Dis. 2013;72(7):1125–1135. [PubMed: 23595142]
40. Pendleton A, Arden N, Dougados M, et al. EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Thera peutic Trials (ESCISIT). Ann Rheum Dis. 2000;59(12):936–944. [PubMed: 11087696]
41. Jordan KM, Arden NK, Doherty M, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteo arthritis: Report of a Task Force of the Standing Committee for Interna tional Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003;62(12):1145–1155. [PubMed: 14644851]
42. Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommen dations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies In cluding Therapeutics (ESCISIT). Ann Rheum Dis. 2005;64(5):669–681. [PubMed: 15471891]
43. Jevsevar DS. Treatment of Osteoarthritis of the Knee: Evidence-Based Guideline, 2nd Edition. JAAOS - Journal of the American Academy of Orthopaedic Surgeons. 2013;21(9):571–576.
44. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis & Rheumatology. 2020;72(2):220–233. [PubMed: 31908163]
45. Kovar PA, Allegrante JP, MacKenzie CR, Peterson MGE, Gutin B, Charl son ME. Supervised Fitness Walking in Patients with Osteoarthritis of the Knee. Annals of internal medicine. 1992;116(7):529–534. [PubMed: 1543305]
46. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA ra doized clinical trial. JAMA. 2013;310(12):1263–1273. [PubMed: 24065013]
47. Reichenbach S, Felson DT, Hincapié CA, et al. Effect of Biomecha cal Footwear on Knee Pain in People With Knee Osteoarthritis: The BIOTOK 2020;323(18):1802–1812. [PubMed: 32396180]
48. Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-re lated ulcer complications. The American journal of gastroenterology. 2009;104(3):728–738. [PubMed: 19240698]
49. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Annals of internal medicine. 2015;162(1):46–54. [PubMed: 25560713]
50. Lee C, Straus WL, Balshaw R, Barlas S, Vogel S, Schnitzer TJ. A compar ison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: a meta-analy sis. Arthritis Rheum. 2004;51(5):746–754. [PubMed: 15478167]
51. Leopoldino AO, Machado GC, Ferreira PH, et al. Paracetamol versus pla cebo for knee and hip osteoarthritis. The Cochrane database of system atic reviews. 2019;2(2):Cd013273. [PubMed: 30801133]
52. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of para etamol for spinal pain and osteoarthritis: systematic review and me ta-analysis of randomised placebo controlled trials. BMJ (Clinical re search ed). 2015;350:h1225.
53. Zhu X, Wu D, Sang L, et al. Comparative effectiveness of glucosamine, chondroitin, acetaminophen or celecoxib for the treatment of knee and/ or hip osteoarthritis: a network meta- analysis. Clinical and experimental rheumatology. 2018;36(4):595–602. [PubMed: 29465368]
54. Cheng OT, Souzdalnitski D, Vrooman B, Cheng J. Evidence-based knee injections for the management of arthritis. Pain Med. 2012;13(6):740–753. [PubMed: 22621287]
55. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial. JAMA. 2017;317(19):1967–1975. [PubMed: 28510679]
56. Deyle GD, Allen CS, Allison SC, et al. Physical Therapy versus Glucocor ticoid Injection for Osteoarthritis of the Knee. The New England journal of medicine. 2020;382(15):1420–1429. [PubMed: 32268027]
57. Conaghan PG, Hunter DJ, Cohen SB, et al. Effects of a Single Intra-Artic ular Injection of a Microsphere Formulation of Triamcinolone Acetonide on Knee Osteoarthritis Pain: A Double- Blinded, Randomized, Place bo-Controlled, Multinational Study. J Bone Joint Surg Am. 2018;100(8):666–677. [PubMed: 29664853]
58. Zeng C, Lane NE, Hunter DJ, et al. Intra-articular corticosteroids and the risk of knee osteoarthritis progression: results from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2019;27(6):855– 862. [PubMed: 30703543]
59. Hochberg MC, Wohlreich M, Gaynor P, Hanna S, Risser R. Clinically Rel evant Outcomes Based on Analysis of Pooled Data from 2 Trials of Du loxetine in Patients with Knee Osteoarthritis. The Journal of Rheumatol

ogy. 2012;39(2):352. [PubMed: 22133624]
60. Osani MC, Bannuru RR. Efficacy and safety of duloxetine in osteoarthri tis: a systematic review and meta-analysis. Korean J Intern Med. 2019;34(5):966–973. [PubMed: 30871298]
61. Enteshari-Moghaddam A, Azami A, Isazadehfar K, Mohebbi H, Habibza deh A, Jahanpanah P. Efficacy of duloxetine and gabapentin in pain reduction in patients with knee osteoarthritis. Clinical rheumatology. 2019;38(10):2873–2880. [PubMed: 31062253]
62. Fleischmann RM, Bliddal H, Blanco FJ, et al. A Phase 2 Trial of Lutikizum ab, an Anti-Interleukin 1alpha/beta Dual Variable Domain Immunoglob ulin, in Knee Osteoarthritis Patients With Synovitis. Arthritis & rheuma tology. 2019;71:1056–1069. [PubMed: 30653843]
63. Kloppenburg M, Peterfy C, Haugen IK, et al. Phase IIa, placebo-con trolled, randomised study of lutikizumab, an anti-interleukin-1alpha and anti-interleukin-1beta dual variable domain immunoglobulin, in patients with erosive hand osteoarthritis. Ann Rheum Dis. 2019;78:413–420. [PubMed: 30552176]
64. Kloppenburg M, Ramonda R, Bobacz K, et al. Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, ran domised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2018;77(12):1757–1764. [PubMed: 30282670]
65. Effects of Interleukin-1□ Inhibition on Incident Hip and Knee Replace ment. Annals of internal medicine. 0(0):null.
66. Yazici Y, McAlindon TE, Fleischmann R, et al. A novel Wnt pathway inhibitor, SM04690, for the treatment of moderate to severe osteoar thritis of the knee: results of a 24-week, randomized, controlled, phase 1 study. Osteoarthritis Cartilage. 2017;25(10):1598–1606. [PubMed: 28711582]
67. Hochberg MC, Guermazi A, Guehring H, et al. Effect of Intra-Articular Sprifermin vs Placebo on Femorotibial Joint Cartilage Thickness in Pa tients With Osteoarthritis: The FORWARD Randomized Clinical Trial. JAMA. 2019;322(14):1360–1370. [PubMed: 31593273]
68. Conaghan PG, Bowes MA, Kingsbury SR, et al. Disease-Modifying Ef fects of a Novel Cathepsin K Inhibitor in Osteoarthritis: A Randomized, Placebo-Controlled Trial. Annals of internal medicine. 202-;172(2):86–95. [PubMed: 31887743]
69. Quality AfHRa. Healthcare Cost and Utilization Project 2014.
70. Katz JN, Losina E, Barrett J, et al. Association between hospital and sur geon procedure volume and outcomes of total hip replacement in the United States medicare population. J Bone Joint Surg Am. 2001;83(11):1622–1629. [PubMed: 11701783]
71. Memtsoudis SG, Della Valle AG, Besculides MC, Esposito M, Koulouvaris P, Salvati EA. Risk factors for perioperative mortality after lower extrem ity arthroplasty: a population-based study of 6,901,324 patient dis charges. The Journal of arthroplasty. 2010;25(1):19–26. [PubMed: 19106028]
72. Mahomed NN, Barrett J, Katz JN, Baron JA, Wright J, Losina E. Epidemi ology of total knee replacement in the United States Medicare popula tion. J Bone Joint Surg Am. 2005;87(6):1222– 1228. [PubMed: 15930530]
73. Inacio MCS, Dillon MT, Miric A, Navarro RA, Paxton EW. Mortality After Total Knee and Total Hip Arthroplasty in a Large Integrated Health Care System. Perm J. 2017;21:16–171.
74. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What pro portion of patients report long-term pain after total hip or knee replace ment for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open. 2012;2(1):e000435.
75. Skou ST, Roos EM, Laursen MB, et al. A Ran domized, Controlled Trial of Total Knee Replacement. New England Journal of Medicine. 2015;373(17):1597–1606.
76. Evans JT, Walker RW, Evans JP, Blom AW, Sayers A, Whitehouse MR. How long does a knee replacement last? A systematic review and me ta-analysis of case series and national registry reports with more than 15 years of follow-up. The Lancet. 2019;393(10172):655–663.
77. Evans JT, Evans JP, Walker RW, Blom AW, Whitehouse MR, Sayers A. How long does a hip replacement last? A systematic review and me ta-analysis of case series and national registry reports with more than 15 years of follow-up. Lancet (London, England). 2019;393(10172):647–654.
78. J asper LL, Jones CA, Mollins J, Pohar SL, Beaupre LA. Risk factors for revision of total knee arthroplasty: a scoping review. BMC musculoskel etal disorders. 2016;17:182–182. [PubMed: 27113334]
79. Prokopetz JJ, Losina E, Bliss RL, Wright J, Baron JA, Katz JN. Risk factors for revision of primary total hip arthroplasty: a systematic review. BMC musculoskeletal disorders. 2012;13:251–251. [PubMed: 23241396]
80. Katz JN, Wright EA, Wright J, et al. Twelve-year risk of revision after primary total hip replacement in the U.S. Medicare population. J Bone Joint Surg Am. 2012;94(20):1825–1832. [PubMed: 23079874]
81. Moseley JB, O'Malley K, Petersen NJ, et al. A Controlled Trial of Ar throscopic Surgery for Osteoarthritis of the Knee. New England Journal of Medicine. 2002;347(2):81–88.
82. Katz JN, Wright J, Spindler KP, et al. Predictors and Outcomes of Cross over to Surgery from Physical Therapy for Meniscal Tear and Osteoarthri tis: A Randomized Trial Comparing Physical Therapy and Surgery. J Bone Joint Surg Am. 2016;98(22):1890–1896. [PubMed: 27852905]
83. Katz JN, Brophy RH, Chaisson CE, et al. Surgery versus Physical Therapy for a Meniscal Tear and Osteoarthritis. New England Journal of Medicine. 2013;368(18):1675–1684.
84. Zhang W, Lyman S, Boutin-Foster C, et al. Racial and Ethnic Disparities in Utilization Rate, Hospital Volume, and Perioperative Outcomes After Total Knee Arthroplasty. J Bone Joint Surg Am 2016;98(15):1243–1252. [PubMed: 27489314]
85. Cavanaugh AM, Rauh MJ, Thompson CA, et al. Racial and ethnic dispar ities in utilization of total knee arthroplasty among older women. Osteo arthritis Cartilage. 2019;27(12):1746–1754. [PubMed: 31404657]
86. Mahomed NN, Barrett JA, Katz JN, et al. Rates and Outcomes of Primary and Revision Total Hip Replacement in the United States Medicare Pop ulation. JBJS. 2003;85(1).
87. Hausmann LRM, Mor M, Hanusa BH, et al. The effect of patient race on total joint replacement recommendations and utilization in the orthope dic setting. J Gen Intern Med. 2010;25(9):982–988. [PubMed: 20509053]
88. Byrne MM, Souchek J, Richardson M, Suarez-Almazor M. Racial/ethnic differences in preferences for total knee replacement surgery. Journal of clinical epidemiology. 2006;59(10):1078–1086. [PubMed: 16980148]
89. I brahim SA, Siminoff LA, Burant CJ, Kwoh CK. Understanding ethnic differences in the utilization of joint replacement for osteoarthritis: the role of patient-level factors. Medical care. 2002;40(1 Suppl):I44–51. [PubMed: 11789631]
90. Nwachukwu BU, Kenny AD, Losina E, Chibnik LB, Katz JN. Complica tions for Racial and Ethnic Minority Groups After Total Hip and Knee Replacement: A Review of the Literature. JBJS. 2010;92(2).
91. Deveza LA, Nelson AE, Loeser RF. Phenotypes of osteoarthritis: current state and future implications. Clinical and experimental rheumatology. 2019;37 Suppl 120(5):64–72. [PubMed: 31621574]
92. Nelson AE, Fang F, Arbeeva L, et al. A machine learning approach to knee osteoarthritis phenotyping: data from the FNIH Biomarkers Con sortium. Osteoarthritis Cartilage. 2019;27(7):994–1001. [PubMed: 31002938]
93. Huang Z, Ding C, Li T, Yu SP. Current status and future prospects for disease modification in osteoarthritis. Rheumatology (Ox ford). 2017;57(suppl 4):iv108–iv123.
94. Jeon OH, Kim C, Laberge RM, et al. Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nat Med. 2017;23(6):775–781. [PubMed: 28436958]
95. Lane NE, Schnitzer TJ, Birbara CA, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. The New England journal of medicine. 2010;363(16):1521–1531. [PubMed: 20942668]
96. Sanga P, Katz N, Polverejan E, et al. Long-Term Safety and Efficacy of Fulranumab in Patients With Moderate-to-Severe Osteoarthritis Pain: A Phase II Randomized, Double-Blind, Placebo-Controlled Extension Study. Arthritis & rheumatology. 2017;69(4):763–773. [PubMed: 27748055]
97. Schnitzer TJ, Easton R, Pang S, et al. Effect of Tanezumab on Joint Pain, Physical Function, and Patient Global Assessment of Osteoarthritis Among Patients With Osteoarthritis of the Hip or Knee: A Randomize Clinical Trial. JAMA : the journal of the American Medical Association. 2019;322(1):37–48. [PubMed: 31265100]
98. Hochberg MC. Serious joint-related adverse events in randomized con trolled trials of anti-nerve growth factor monoclonal antibodies. Osteo arthritis Cartilage. 2015;23 Suppl 1:S18–21. [PubMed: 25527216]
99. Chapple CM, Nicholson H, Baxter GD, Abbott JH. Patient characteristics that predict progression of knee osteoarthritis: a systematic review of prognostic studies. Arthritis Care Res (Hoboken). 2011;63(8):1115–1125. [PubMed: 21560257]
100. Bastick AN, Runhaar J, Belo JN, Bierma-Zeinstra SMA. Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies. Arthritis Research & Therapy. 2015;17(1):152. [PubMed: 26050740]
101. Treatment of Osteoarthritis of the Knee: Evidence-Based Guideline. In: Surgeons AAoO, ed. 2nd ed 2013.
102. Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non- pharmacological core management of hip and knee osteoar thritis. Ann Rheum Dis. 2013;72(7):1125–1135. [PubMed: 23595142]

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Pharmacotherapy for knee osteoarthritis: Current and emerging therapies

ABSTRACT :

Introduction: Osteoarthritis (OA) is the leading cause of pain, loss of function and disability in the elderly, with the knee being the most impactful joint affected. Currently, there is still no 'cure' in OA treatment.

Areas covered: The authors review the current and emerging therapies for knee OA including traditional OA medications (oral and topical NSAIDs, acetaminophen, and opioids) and emerging treatments including disease-modifying OA drugs. The failures of agents that have been through clinical trials are also summarized. Furthermore, the authors provide their expert perspectives on the future of pharmacotherapy for knee osteoarthritis.

Expert opinion: Compared to traditional OA medications, new disease-modifying OA drugs that act by reducing inflammation and increasing cartilage repair show promise to address the unmet need of disease modification. Many of these new drugs, however, are in the preclinical stage. Long-term RCTs are expected to identify the safety and efficacy of novel OA pharmacotherapy medicines.

1. INTRODUCTION

Osteoarthritis (OA) is the leading cause of pain, loss of function, and disability in the elderly and mainly affects the joints of the knee, hand, and hip [1]. OA pathogenesis is believed to involve both biomechanical and biochemical factors, which poses a crucial challenge to the effective treatment of OA [2]. OA reflects failure of the synovial joint organ and is a whole organ disease prominently affecting tissues including cartilage, subchondral bone, and synovium [3]. At present, there is no cure for OA and the currently available therapies are modest in their effect and often have a range of limiting side-effects [4]. The current treatments mainly focus on reducing pain and other symptoms, as well as improving joint functional capacity [5]. Along with a better understanding of pathological processes, some emerging disease-modifying therapies have been studied and hold promise for future OA management [6–8]. In this narrative review, we will discuss current pharmacological treatments for OA patients, including traditional pharmacological treatments recommended by guidelines, as well as provide an update on recent developments of emerging medications with a focus on diseasemodifying OA drugs.

2. Traditional management

Over the last few years, the Osteoarthritis Research Society International (OARSI) [9], American College of Rheumatology (ACR) [10], National Institute for Health and Care Excellence (NICE) [11], American Academy of Orthopaedic Surgeons (AAOS) [12], European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) [13], and others have developed and updated recommendations through Clinical Practice Guidelines for improving the treatment of knee OA. Most guidelines are consistent in advocating for non-pharmacologic treatments as the core of initial interventions including exercise, weight loss, and education. Appropriate exercises increase muscle strength to optimize joint function [14]. For those who are overweight, weight loss is promoted [15]. Traditional pharmacological interventions have focused on symptom management and the most widely used agents include oral and topical non-steroidal anti–inflammatory drugs (NSAIDs), acetaminophen, and opioids. It is important torecognize that acetaminophen is no longer the first-line analgesic recommended in guidelines due to limitations in effect and a range of unwanted side-effects [16,17]. In addition, opioids whilst widely used have harms that outweigh the benefits along with a range of societal concerns including overdoses and deaths; therefore, the recent OARSI guideline has proposed 'Level 4A' evidence (≥75% 'against' and >50 'conditional' recommendation) for opioids to treat knee OA without comorbidities [9,18]. There is a range of pharmacologic interventions available for the management of knee OA that have been advocated by most guidelines (Table 1).

2.1. NSAIDs

NSAIDs are frequently used in the treatment of symptomatic knee or hip OA. The mechanism of action of NSAIDs is to provide the suppression of cyclooxygenase enzymes activity, leading to decreased synthesis of prostaglandins resulting in analgesia. In a large meta-analysis, Bjordal et al. reviewed 10,845 knee OA patients from 23 trial [19]. A relatively small effect size of NSAIDs for pain reduction of 0.23 (0.15 to 0.31) was reported in knee OA during short-term use between 2 and 13 weeks. Similarly, in another meta-analysis, NSAIDs demonstrated a small-to-moderate effect size of 0.29 (0.22 to 0.35) in the treatment of pain in OA [20].

Compared to oral NSAIDs, topical application of NSAIDs showed better tolerability properties due to reduced side effects compared with the oral format [21]. In the recent OASRI guideline, topical NSAIDs were strongly recommended for use in knee OA patients with no comorbidities [9]. A study by Kinsler et al. supported that use of topical NSAIDs, such as diclofenac, for pain relief in OA affecting a single joint or a small number of joints is

Article highlights

Most guidelines are consistent in advocating for non-pharmacologic treatments as the core ofinitial interventions including exercise, weight loss and education.
Traditional pharmacological interventions have focused on symptom management and the most widely used agents include oral and topical non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids.
Pain is the dominant symptom of OA, is still an unmet need and recent years have witnessed several prominent clinical trials for OA pain, and among those, trials with antibodies that neutralize nerve growth factor (NGF) appear particularly promising.
A drug that inhibits the structural disease progression of OA with symptomatic relief, is defined as a disease-modifying osteoarthritis drug (DMOAD). A number of promising agents are being developed in this area.
Numerous agents have been tested and developed for purported DMOAD activity and failed-important lessons have been learned which had been applied in more recent trials.

appropriate and limits the risk of side effects [22]. According to Kinsler et al.'s study, topical diclofenac solution even in lower blood level could demonstrate the same efficacy in pain alleviation as oral NSAIDs [22].

Although studies have supported NSAIDs with overall improvement on pain relief, the consistent NSAIDs-induced side effects greatly limit its widespread use. For people taking NSAIDs, it is estimated that the incidence of side effects is about 30% [23]. The risk of gastrointestinal (GI) complications, one of the most common side effects that occur every year in 1–2% of people who use NSAIDs, was increased by three to fivefold [24]. There are also reports of kidney disease and adverse cardiovascular events associated with the use of NSAIDs [25,26]. An important, large individual patient data-meta-analysis including 446,763 persons in 2017 reported that all NSAIDs were found to be associated with an increased risk of acute myocardial infarction [25]. They also documented that the increased risk of myocardial infarction occurs in the first week of exposure to an NSAID [25]. Therefore, NSAIDs should be given at the lowest effective dose and for the shortest time needed to minimize adverse events when approved for use.

2.2. Acetaminophen

Acetaminophen, commonly referred to as paracetamol, has long been regarded as a mainstay of knee OA treatment for people with mild to moderate OA by all guidelines. While acetaminophen is widely used for OA analgesia, its overall effectiveness is low, and its use is motivated by belief in its relative safety and a lack of effective or acceptable alternative pharmacotherapies [27]. Acetaminophen has limited effects on cyclooxygenase (COX)-1 and COX-2 inflammatory factors that are necessary for prostaglandin synthesis (PGs) [28]. It has been reported that acetaminophen was significantly superior to placebo in terms of overall pain reduction from 7 rando- mized controlled trials (RCTs) [29]. However, no significant differences in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were found between acetami-nophen and placebo from these RCTs.

Recent meta-analysis suggested that acetaminophen had little to no efficacy in patients with OA, with a signal for possible hepatotoxicity [17]. At short term of 3 weeks' to 3 months' follow-up, there was high-quality evidence from 8 RCTs that acetaminophen provided no clinically important improvements in pain and physical function. Abnormal liver function tests were more likely to occur with acetaminophen (RR: 3.79, 95% CI: 1.94 to 7.39), but the evidence was downgraded due to the wide CIs and imprecise effect estimates. Therefore, according to the latest OARSI guideline, the

Key points

- Long characterized as a 'wear and tear' disorder, osteoarthritis (OA) is now understood to have a complex pathophysiology affecting multiple joints and joint structures, as captured by the Osteoarthritis Research Society International definition of OA:
- "The disease manifests first as a molecular derangement (abno mal joint tissue metabolism) followed by anatomic, and/ or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness."

Table 1. Pharmacologic recommendations from OARSI, AAOS, ACR, ESCEO, and NICE guidelines for knee OA.

Organization	Acetaminophen or paracetamol (<4 g/day)	Oral NSAID-nonselective	Oral NSAID (Cox-2 Inhibitors)	Topical NSAID	Glucosamine and/or chondroitin	Gastroprotection for high-risk patients[f]	Tramadol	Capsaicin	Opioids	Duloxetine	Diacerhein	Avocado Soybean unsaponifiables	Intra-articular corticosteroids	Intra-articular hyaluronic acid
OARSI (Knee)[a]	4A	1B	1B	1A	4A			4B	4A	3	4A	3	1B	2
AAOS[b]	I	S		S	NR-S		S		I				I	NR-S
ACR (Knee)[c]	CR	SR		SR	SRA		CR	CR	CRA	CR			CR	CRA
ESCEO[d]	WRN	SR	SR	SR	SR				WR	WR	SR	SR	WR	WR
NICE[e]	R	R	R	R	NR	R	R	R	R				R	NR

[a]OARSI recommendation levels: Level 1A- ≥75% 'in favor' & >50% 'strong' Recommendation; Level 1B- ≥75% 'in favor' & >50% 'conditional' Recommendation; Level 2- 60%-74% 'in favor'; Level 3- 40%-59% 'in favor'; Level 4A- ≥75% 'against' & >50% 'conditional' Recommendation; Level 4B- 60%-74% 'against'.

[b]AAOS recommendation grades: Strong (S, high-quality evidence), Moderate (M, moderate quality), Limited (L, low quality), Inconclusive (I), or Consensus (C). NR = not recommended.

[c]ACR recommendation grades: A strong recommendation (SR) required high-quality evidence and a large gradient of difference between desirable and undesirable treatment effects. A conditional recommendation (CR) was based on the absence of high-quality evidence and/or evidence of only a small gradient of difference between desirable and undesirable treatment effects. CRA = conditionally recommended against. SRA = strongly recommended against.

[d]ESCEO recommendation grades: Strong recommendation (SR), Weak recommendation (WR), Weak recommendation against (WRA), Strong recommendation against (SRA).

[e]NICE recommends (R) treatments based on grading of evidence and formal consensus.

[f]COX-2, topical over oral NSAID, or add PPI or another agent.

use of acetaminophen was con-ditionally not recommended with level 4A and 4B evidence.

2.3. Opioids

Currently, most guidelines do not advocate for long-term use of opioids [30]. The mechanism of action of opioids on OA is to inhibit the central nervous system pain pathway by binding the mu-opioid receptor [31]. However, use of opioids is discouraged due to the serious side effects, such as nausea, vomiting, dizziness, drowsiness, constipation, and headache [18]. It is reported from a large meta- analysis of 18 RCTs that over 25% of opioid group patients withdrew from studies [32]. Moreover, long-term use of opioids may be associated with potential tolerance, addiction, accidental overdose, and even death. A study showed that in 2014, opioid addiction increased with nearly 2.5 million adults affected in the US [33]. At the same time, opioid overdose deaths also significantly increased. The recent OARSI guideline strongly recommended against the use of either oral or transdermal opioids in patients with knee OA, largely in response to recent global concerns about the devastating potential for chemical dependency of opioid medications [9].

3. Emerging treatments

3.1. Symptom-relieving drugs

Pain is the dominant symptom of OA and is the main reason people seek care and an important determinant of their ongoing management success. NSAIDs and other analgesics are widely used clinically to relieve pain. However, the avail- able drugs have side effects or toxicity profiles that are not suitable for long-term use. Therefore, there is a great need to develop agents that effectively control OA pain. With a better understanding of the pathophysiology of OA pain, it has been recognized that refractory pain associated with OA may origi- nate from neurogenesis and may respond to neutralizing specific neurotransmitters [34,35]. As a result, duloxetine, a selective serotonin and norepinephrine reuptake inhibitor with central nervous system activity, is increasingly used for the treatment of musculoskeletal pain, including OA [36].

Recent years have witnessed several prominent clinical trials for OA pain, and among those, trials with antibodies that neutralize nerve growth factor (NGF) appear particularly promising. NGF is a key mediator of acute and chronic pain and its expression is markedly increased in pain conditions [37]. Monoclonal antibodies to NGF can down-regulate the binding of NGF to its receptor, and block its biological activity [38]. These antibodies have entered clinical trials, including tanezumab, fasinumab, and fulranumab. Of those, tanezumab has been the most extensively studied and has completed phase III trials. Fulranumab has been reported to be well tolerated and efficacious for pain relief, while Janssen announced discontinuation of it in 2016. Fasinumab is in the midst of phase 3 clinical trials. Recently, the FDA has granted Fast Track designation (a process designed to facilitate the development and expedite the review of new therapies to treat serious conditions and fill unmet medical needs) for tanezumab for the treatment of OA pain and chronic low back pain (Table 2).

The first large randomized double-blind controlled trial of tanezumab (NCT00394563) for OA pain in 2010 revealed dramatic pain relief among many patients [39]. It was reported that tanezumab in doses of 5 and 10 mg were statistically significantly superior to NSAIDs or opiates, with standardized effect sizes of 0.22–0.24. Chen et al. reported that tanezumab low-dose (≤2.5 mg) treatment had comparable efficacy to high dose, but with significantly fewer adverse effects [40]. Recently, a phase-III, randomized, double-blind, placebo- controlled multi-center study (NCT02697773) assessed the efficacy and safety of tanezumab among patients with moderate to severe OA of the knee or hip and inadequate response to standard analgesics [41]. Tanezumab, compared with placebo, showed statistically significant improvements in scores assessing pain and physical function, although the improvements were modest and tanezumab-treated patients had more joint safety events and total joint replacements.

The FDA placed a hold on all clinical trials of NGF antago-nists in 2012 because tanezumab was found to be associated with rapid OA progression and a rare adverse effect, osteo-necrosis. Mullard et al. reported a dose–response relationship between osteonecrosis and doses of tanezumab between 2.5, 5, and 10 mg [42]. Rapidly progressive OA appears to be dose-dependent with doses of tanezumab between 2.5 and

Key points

- The lifetime risk of symptomatic knee OA is greater in obese persons (BMI ≥ 30 kg/m2) than nonobese persons (19.7% versus 10.9%). Prior joint trauma, such as anterior cruciate ligamentrupture and ankle fracture, increases risk, accounting for 12% of knee OA cases.
- The prevalence of symptomatic, radiographic knee OA was 11.4% in women and 6.8% in men in one large cohort study and 18.7% in women and 13.5% in men in another large cohort study. As compared to males with OA, women have more severe radiographic findings and symptoms.

Key points

- OA as well as knee OA. In addition, congenital and acquired anatomic abnormalities (e.g. hip dysplasia) are risk factors for hip OA. Regarding race, African Americans and whites have similar prevalence of hip OA (accounting for race, sex and body mass index), while African Americans, especially women, have higher prevalence of knee OA.

10 mg [43], and with doses of fasinumab between 3 and 9 mg [44]. Therefore, trials were resumed in 2015 with tane- zumab use under the dose of 5 mg. Of note, tanezumab administered with NSAIDs increased the risk of rapid progression of OA [43,45]; therefore, the duration of NSAIDs use during anti-NGF treatment was severely limited in subse quent trials. Cost-effectiveness analyses suggest that rapid OA progression at rates observed in clinical trials, even at a rate of 10%, does not lead to an overall decrease in quality adjusted life expectancy [46]. Future studies are warranted to determine the appropriate role of NGF antibodies in the treatment of OA, specifically at what part of the disease continuum these agents are appropriate, particularly given their cost and side-effect profile.

3.2. Disease-modifying drugs

OA is a complex condition and that disease onset may be triggered by pathology in multiple tissues. Therefore, there is no single drug that can be used for the treatment of all OA patients. A drug that inhibits the structural disease progression of OA with symptomatic relief was defined as a disease-modifying osteoar thritis drug (DMOAD). According to regulatory guidelines from the US FDA and the European Medicines Agency (EMA), the approval of a DMOAD requires a slowing in the loss of knee or hip joint space width (JSW) on x-ray with relevant symptomatic benefit.

DMOADs provide the promise of controlling the structural progression of OA by targeting cartilage metabolism/catabolism, subchondral remodeling, and inflammation [8]. Emerging drugs targeting articular cartilage molecular mechanisms seem to be promising since cartilage damage is a central part of OA pathogenesis (Table 3).

3.3. FGF-18 (Sprifermin)

Fibroblast growth factor 18 (FGF-18) binds to its receptor in cartilage and stimulates chondrogenesis and cartilage matrix production [47,48]. Sprifermin is a synthetic form of human FGF-18. A randomized, double-blind, placebo-controlled, proof-of-concepttrial was conducted in 180 patients with symptomatic knee OA[49]. Intra-articular (IA) sprifermin was proved to have no statistical significance in reducing cartilage loss in the central medial femorotibial compartment or improvement in symptoms but was associated with statistically significant, dose-dependent reductions in loss of total and lateral femorotibial cartilage thickness and volume. However, a post-hoc analysis of the same study revealed that patients after intra-articular sprifermin showed less worsening of cartilage loss and improvement of BMLs at 12 months [50]. Another post-hoc analysis performed by Eckstein et al. demon strated that intra-articular sprifermin (100 µg) not only increases cartilage thickness but also reduces cartilage loss [51]. Another post-hoc analysis to evaluate cartilage thickness changes and symptomatic outcomes in an 'at risk' subgroup with higher pain scores and lower joint space width (JSW) at baseline demonstrated structural improvement with sprifermin was maintained, and WOMAC score improvements vs placebo increased over time and were significant at 3 years [52]. This supports further studies of sprifermin as a potential DMOAD in target populations. In contrast, Dahlberg et al. found no significant changes in cartilage parameters measured by MRI or X-ray between sprifermin and placebo groups [53], probably due to the small sample size (n = 55) and short observation period (24 weeks). Recently, a dose-finding, multicentre randomized trial (NCT01919164) of patients with symptomatic radiographic knee OA reported that intra-articular administration of 100 µg of sprifermin every 6 or 12 months resulted in an improvement in total femorotibial joint cartilage thickness after 2 years [54].

3.4. Gene therapy

Gene transfer technologies are used to either overexpress therapeutic factors such as growth or transcription factors or to suppress the expression of genes that support the OA, rather than replacing or repairing an abnormal gene that causes the disease [55]. Gene therapy approaches should consider the distinct stages and phenotypes of OA [55]. Tissue Gene-C delivers human allogeneic chondrocytes expressing transforming growth factor (TGF)-1 directly to the injured knee joint [56]. Results from the two phase-II trials [57,58] (NCT01221441, the other not registered on ClinicalTrial.gov) and one phase-III trial [59] (NCT02072070) reported that patients treated with Tissue Gene-C showed trends of struc-tural improvement, but these were not statistically significant ($p > 0.05$). However, it demonstrated a statistically significant improvement in pain and function. This product is currently on hold by the FDA pending further investigations

Table 2. Active NGF antibody programs for OA pain in Phase III trials.

Antibodyname(s)	Target	Active trial IDs	Completed trial IDs
Tanezumab	NGF	NCT03031938	NCT02709486; NCT02697773; NCT00863304; NCT00744471; NCT00830063; NCT00733902; NCT02528188; NCT02674386
Fasinumab	NGF	NCT03161093; NCT02683239; NCT03304379; NCT02447276; NCT03245008	NCT03285646

into the cell lines being used.

3.5. Wnt/ß-catenin signaling pathway inhibitors

SM04690 is a novel small-molecule Wnt pathway inhibitor. It has a dual mechanism of action with three specific effects on joint health-generation of articular cartilage, slowing down cartilage degradation, and reducing inflammation in the joint [60]. Data from a phase I clinical trial (NCT02095548) suggested that SM04690 had potential as a DMOAD [61]. The preliminary results of a phase II study of SM04690 (NCT03122860) reported at the 2017 ACR Meeting that a significant improvement in pain and function with a trend of maintaining mJSW was observed. Another SM04690 phase II study presented at 2018 EULAR Congress reported that patients treated with 0.07 mg SM04690 showed statistically significant improvements in pain, compared to placebo at weeks 39 (P = 0.043) and 52 (P = 0.027). In addition, a phase III clinical study (NCT03928184) to evaluate the long-term efficacy and safety of SM04690 in the treatment of knee OA has been initiated, and preliminary results are expected to be obtained in 2020. If it can be further confirmed that intramus- cular injection of SM04690 can slow cartilage degradation and promote new cartilage formation, SM04690 is likely to become a potential DMOAD.

3.6. MMPs/ADAMTs

The Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases belonging to the metzincin superfamily [62]. They are believed to be involved in articular cartilage collagen breakdown [63]. Therefore, MMP inhibitors have been proposed as potential pharmacological therapies for OA management [64]. MMP-13 is one of the selective MMPs inhibitors that may be an attractive therapeutic strategy for OA treatment. Previous studies have identified that MMP-13 plays an important role in the progression of cartilage damage [65,66]. Highly selective MMP-13 inhibitors such as ALS 1–0635 and PF152 have shown benefits in slowing disease progression in preclinical trials [67,68]. However, limited data are available on the role of MMP-13 inhibitors in the treatment of OA and human clinical trials are still required to observe the effectiveness of MMP-13 inhibitors as a DMOAD.

Aggrecanases, also known as a disintegrin and metallopro- teinase with thrombospondin motifs (ADAMTs), are another class of metalloproteinases targeting aggrecan [69]. ADAMTS-4 and ADAMTs-5 are two key members from the ADAMTs family that are involved in cartilage degradation [70]. AGG-523 was the first selective oral aggrecanase inhibitor of ADAMTs-4 and ADAMTs-5 that has entered phase 1 clinical trials (NCT00454298 and NCT00427687), but the trials were suspended for unknown reasons [71]. The anti-ADAMTS-5 nanobody®, M6495, showed protection against cartilage breakdown in cartilage and syno

Key points

- OA is commonly associated with comorbidities, which may stem from lack of physical activity, medication toxicity, and the effects of inflammatory cytokines. It has been estimated that 31% of persons with OA have ≥5 comorbid conditions. Persons with hip and knee OA have ~20% excess mortality as compared with age-matched controls, due in part to lower levels of physical activity.
- OA arises from complex biological processes that include cartilage, bone, synovium, ligaments, periarticular fat, meniscus, and muscle. The classic features of OA noted on radiographs include joint space narrowing due to loss of articular cartilage and meniscus, and bony changes including sclerosis of subchondral bone and osteophytes. The effects of OA on cartilage, meniscus, syovium, subchondral bone and other structures can be appreciated on magnetic resonance imaging.

Key points

- OA consists of multiple phenotypes. Knee OA developing after anterior cruciate ligament tear might have a mechanism distinct from OA associated with obesity. Individuals may have more than one mechanism at play, requiring multi-modal management.
- It will be important to determine which individuals with early OA are more likely to progress rapidly and would benefit from an intervention designed to slow disease progression. Machine learning approaches using datasets that include demographic, imaging and biomarker data are being harnessed to identify such subsets.

vial joint tissue explant models after in vitro studies, are currently awaiting results from phase I (NCT03224702) and phase Ib clinical trials (NCT03583346) [72].

3.7. Senolytic agents

Aging is an important risk factor for most chronic diseases and functional deficits in human. The senescent cells accumulate in various tissues and organs with aging and have been hypothesized to disrupt tissue structure and function [73]. Therefore, removing senescent cells from joints may be a potential treatment for OA [74,75]. UBX0101, which is a small-molecule senolytic compound, is one of the most notable senolytic agents tested successfully in preclinical studies [76]. UBX0101 reduced the expression of senescence associated secretory phenotype (SASP) factors and improved overall joint function. Several randomized, controlled clinical trials of UBX0101 are currently ongoing to evaluate the efficacy, safety, and tolerability of intra-articular administration of UBX0101 in OA patients (NCT03513016, NCT04129944, and NCT04229225).

3.8. Mesenchymal stem cells (MSCs)

There is considerable controversy in the MSCs in OA area and the claims of MSCs having the hallmarks of 'quack medicine' [77] (desperate patients, pseudoscience, and large amounts of money being charged for unproven therapies) there is a great need for clarity of evidence to resolve this debate. Recently, several systematic reviews or meta-analyses concerning this topic have been published. The most comprehensive and robust of these systematic reviews identified 18 clinical trials on this topic, including 10 single-arm prospective studies, four quasi-experimental studies and 4 RCTs treating a total of 565 patients with OA [78–80]. This meta-analysis demonstrated superiority for symptoms following MSCs intervention at 12 and 24 months. However, after excluding the data from quasi experimental and single-arm uncontrolled prospective studies and only using the data from RCTs (n = 4), the treat- ment of MSCs did not demonstrate superiority. There was clear evidence of publication bias and remarkable hetero- geneity in methods of MSC preparation (often incompleely described) and concentration of MSCs with the vast majority of studies only including older patients with knee OA. Seven of the 18 trials reported adverse events after MSC treatment, in which the predominant symptoms were local swelling and transient regional pain. There was no clear evidence of structural effects, but the studies that have investigated this have found evidence suggestive of an effect [81]. There does appear to be a dose–response relationship and advanced disease does not appear to be responsive. This was further highlighted in a systematic overview of the systematic reviews which reinforced the need for high-quality clinical studies with rigorous standardized methodology [82]. Ultimately, the lack of clear conclusions highlights the need for adequately powered, rigorous RCTs.

4. Summary of failures

For many of the agents highlighted in the prior section that are progressing toward late-stage development, they have learned pivotal lessons from previous trial failures. These include the recognition of structure and symptom discordance and the challenges in meeting symptom thresholds for improvement. The disease itself is incredibly heterogeneous and we have traditionally focused on people with end-stage disease where pharmacologic interventions may have limited effects. The repeated failures to translate from preclinical models into the human conditions are reported, because the fact that one does not mimic the other is increasingly recognized. This section will focus on agents that have been through disease-modifying trials and have failed on one or other primary outcome.

4.1. Bisphosphonates

Bisphosphonates, such as alendronate, risedronate, and zoledronic acid, were reported to have beneficial effects in improving symptoms and decreasing subchondral bone lesions from several observational studies [83]. Two case– control studies have demonstrated a delay of total knee joint replacement for elderly with OA after the treatment of bisphosphonates, in particular, if used in the long term [84,85]. However, the result was controversial because the rate of knee replacement depends not only on OA severity but also on patient preference. Recently, a meta-analysis concluded that the treatment of bisphosphonates contributes no significant benefit in knee OA patients in terms of alleviating pain, improving function, or preventing radio- graphic progression compare to placebo controls [86]. The failure of these RCTs might due to the re

Table 3. The registered phase II and III clinical trials on compounds with potential disease-modifying effects on cartilage.

Drug Class/Compound	ClinialTrials.gov identifier	Company	Structure	Targeted tissue	Mechanism of action	Stage of development
Fibroblast Growth Factor (FGF-18) Sprifermin (AS902330)	NCT01919164	Merck KGaA (Germany)	Recombinant human fibroblast growth factor 18 (rhFGF18)	Cartilage regeneration and repair	Stimulating chondrogenesis and cartilage matrix production through fibroblast growth factor receptor-2 and 3	Phase II (completed in 2018)
Gene Therapy TissueGene-C	NCT01221441	Kolon TissueGene, Inc.	Allogeneic human chondrocytes modified to express transforming growth factor (TGF)-β1	Cartilage regeneration and repair	Stimulating the regeneration of damaged degenerate cartilage or regrowing lost cartilage	Phase II (completed in 2014)
	NCT02072070	Kolon Life Science (South Korea)				Phase III (completed in 2015)
	NCT03291470	TissueGen, Inc. (USA)				Phase III (Not yet recruiting; estimated to be completed in 2021)
Wnt/ß-catenin signaling pathway inhibitors SM04690	NCT03122860	Samumed LLC (USA)	N-(5-(3-(7-(3-Fluorophenyl)-3 H-imidazo(4,5-C) pyridin-2-yl)-1 H-indazol-5- yl)-pyridin-3-yl)-3-methylbutanamide	Cartilage catbolism	Induction of protease production, especially, matrix metalloproteinases	Phase II (completed in 2018)
	NCT03928184					Phase III (recruiting; estimated to be completed in 2020)
	NCT02536833					Phase II (completed in 2017)
	NCT03727022					Phase II (recruiting; estimated to be completed in 2020)
	NCT03706521					Phase II (recruiting; estimated to be completed in 2020)
Matrix Metalloproteinase (MMP) inhibitors PG-116,800	NCT00041756	Procter and Gamble (USA)	2-((4-(4 methoxybenzamido) phenyl) sulfonamido)-6-morpholinohex-4-ynoic acid	Cartilage catabolism	Inhibiting the zinc-dependent matrix metalloproteinases	Phase II (completed in 2004)
Doxycycline	NCT00000403	Indiana University	A synthetic tetracycline derivative	Cartilage catabolism	Partly mediated by inhibiting metalloproteinase activity	Phase III (completed in 2001)
Senolytic agents UBX0101	NCT04129944	Unity Biotechnology, Inc.	a small-molecule senolytic compound	Cartilage regeneration	Clearing senescent cells	Phase II (recruiting; estimated to be completed in 2020)
Mesenchymal stem cells (MSCs)	NCT03818737	Emory University	Multipotent cells capable of differentiating into osteocytes, adipocytes, chondrocytes and other cells underdefined conditions	Cartilage regeneration and repair	Facilitating cartilage regeneration and repair by releasing cytokines	Phase III (recruiting; estimated to be completed in 2021)
	NCT03990805	R-Bio				Phase III (recruiting; estimated to be completed in 2020)
	NCT04230902	American University of Beirut Medical Center				Phase III (recruiting; estimated to be completed in 2021)
	NCT03467919	Stanford University				Phase III (recruiting; estimated to be completed in 2020)

Key points

- Osteoarthritis (OA) is the leading cause of pain, loss of function, and disability in the elderly and mainly affects the joints of the knee, hand, and hip. OA pathogenesis is believed to involve both biomechanical and biochemical factors, which poses a crucial challenge to the effective treatment of OA.
- OA reflects failure of the synovial joint organ and is a whole organ disease prominently affecting tissues including cartilage, subchondral bone, and synovium. At present, there is no cure for OA and the currently available therapies are modest in their effect and often have a range of limiting side-effects.

cruitment criteria of patients with too advanced OA for bisphosphonates therapy. Currently, a randomized, controlled clinical trial is ongoing to evaluate the efficacy and safety of intra-articular clodronate for knee OA (EudraCT 2018-002081-39).

4.2. Vitamin D

Vitamin D deficiency was found to be associated with the development and progression of knee OA, including cartilageloss, increased radiographic joint space narrowing (JSN) and pain [87]. However, whether vitamin D supplements can reduce OA pain remains controversial. A meta-analysis of 4 RCTs showed that vitamin D supplementation significantly improved WOMAC pain and loss of function, albeit not of a clinically significant magnitude and demonstrated no effect on WOMAC stiffness nor tibial cartilage volume [88]. Another RCT revealed that vitamin D supplementation significantly reduced knee pain and improved function than placebo control [87]. It is possible that the treatment of vitamin D supplementation is effective for vitamin D deficiency patients [89], those with low vitamin D response index [90], those with inflammatory phenotype [91], and/or those who are not obese [92].

4.3. Interleukin-1 (IL-1) inhibitor

IL-1 is expressed in the cartilage, synovium, and synovial fluid of OA patients [93]. It is involved in OA progression by stimulating the synthesis of mediators such as proteolytic enzymes and cytokines [94]. Therefore, several RCTs were conducted to explore whether IL-1 could be the potential approach for OA. In one study, an IL-1 receptor antibody of AMG108 was intraarticularly injected into 159 patients with knee OA once 4 weeks for 12 weeks [95]. No statistically significant differences were found between AMG108 group and the placebo group in terms of pain release.

4.4. Inducible NO synthase (iNOS) inhibitors

The iNOS can produce nitric oxide (NO) and leads to the activation of MMPs, the inhibition of proteoglycan and collagen synthesis and the enhancement of inflammation [96]. The Cindunistat study (NCT00565812) was sponsored by Pfizer and targeted persons with medial tibiofemoral OA [97,98]. The efficacy of SD-6010 was evaluated by radiography using joint space narrowing in the medial tibiofemoral compartment of the study knee as the primary endpoint. A total of 1400 per-sons were enrolled in the main cohort (X-ray + Outcome Measures) and 100 persons were enrolled in an MRI subcohort (patients who underwent MRI of the knee); blood and urine samples were also collected from the small MRI subcohort. The duration of the trial for individual participants was 22 months. This study failed to show a reduction of JSN in knee OA.

4.5. Strontium ranelate

Strontium ranelate is an anti-osteoporotic drug which can increase bone formation, decrease bone resorption, and reduce cartilage degeneration [99,100]. Strontium ranelate Efficacy in Knee Osteoarthritis trial (SEKOIA), a 3-year multi- centre, double-blind, randomized, placebo-controlled trial, was designed to evaluate the effect of strontium ranelate on radiological and clinical progression of knee OA [101]. The primary endpoint was radiographic change in JSW (medial tibiofemoral compartment) over 3 years versus placebo. The SEKOIA study showed that treatment with strontium ranelate for 3 years was associated with a beneficial effect on knee structure at a dose of 1 and 2 g/day and on symptoms at a dose of 2 g/day in knee OA patients.

It does demonstrate clearly that disease modification is possible and the outcomes on both radiological and clinical progression of knee OA appear to be of clinical significance. However, Servier is no longer manufacturing strontium rane late because of concerns over cardiovascular safety and specifically thromboembolic side effects [102].

4.6. Steps to overcome these barriers

To date, there are no effective disease-modifying therapies that have been approved by regulatory bodies, and most patients are not satisfied with available symptom-modifying drugs due to their modest effects and toxicity. As previously mentioned, there are some potential barriers to overcome in the production of effective OA therapeutics, because OA is a heterogeneous condition characterized by complex and multifactorial etiologies, there is still not consensus on trial endpoints.

There are many obstacles related to biomarker validation and qualification in OA research and drug development. In 2010, a working group that included biomarker experts from acade-mia, NIH, FDA, and industry was established. The immediate focus of

this group was to use standardized methods for biomarker validation and qualification in OA, and then with shared purpose, pursue the validation of specific biomarkers [103]. The overarching OA Biomarker project objective is to establish the predictive validity of disease progression biomarkers and assess the responsiveness of several imaging and biochemical markers pertinent to knee OA within the OAI study, which is a multi-center, longitudinal, prospective observational study focusing primarily on knee OA in 4796 persons aged 45–79 years [104].

OARSI submitted a White Paper entitled Osteoarthritis as a Serious Disease to the FDA on 1 December 2016. Since then, the FDA has recently expanded the definition of a serious condition. The white paper provided an extensive review of the epidemiology of OA, impact on the quality of life, related symptoms and functional disabilities, and association with increased co-morbidity risk and mortality. An additional systematic review of clinically relevant outcomes in OA was undertaken to establish the argument that biomarkers (bio-chemical and/or imaging) used as intermediate endpoints can serve as surrogates of structural change [105]. Confirming OA as a serious disease was an important step for consideration of allowing the use of surrogate markers in the development of structure-modifying therapies.

Encouragingly, the FDA acknowledged that OA can be a serious disease with an unmet medical need for therapies in their latest guidance document. This formal recognition supports the potential use of surrogate endpoints for regulatory approval of a drug or biologic under FDA's accelerated approval regulations. However, the use of surrogates or intermediate clinical endpoints for initial regulatory approval of a drug or biologic requires confirmation in a post-marketing study of a drug effect on a clinically relevant outcome [106]. Therefore, post-marketing confirmatory studies need to be properly designed. So far, there have been a moderate number of accelerated drug approvals for serious diseases and these provide insights into possible study designs and end points for use in OA trials.

5. Special considerations

In the past few years, it is increasingly appreciated that OA is a heterogeneous condition with different phenotypes, due to various disease mechanisms, structural abnormalities, clinical features, and treatment response. However, there is still no consensus regarding specific OA subgroups. In addition, there is evidence of the discordance between radiographic severity and pain in OA [107], which implied that factors beyond joint pathology, such as pain sensitization, psychological factors, and high co-morbidities, may also contribute to joint pain [108]. Thus, it is difficult to find a very effective therapy that may be generalizable for all patients. Therefore, future study should aim to classify OA patients into various phenotypes and develop a tailored therapy according to specific factors involved in the pathogenesis of the disease and the clinical features of each patient.

Furthermore, for chronic diseases, such as OA, patients often need long-term medication; therefore, drugs should not only demonstrate early efficacy but also ensure that the efficacy is sustainable and safe enough to balance the need for treatment progression.

Over the past decade, glucosamine (GS) and chondroitin sulfate (CS) have been widely used for the management of symptoms of OA [109]. Several RCTs demonstrated that when using joint JSW or cartilage volume loss (CVL) as outcome measures, single use of GS or CS could have small to moderate structural protective effects in patients with OA [110–112]. Martel-Pelletier et al. demonstrated that the combination of GS/CS and NSAIDs had reduced CVL over 24 months in subregions when assessed with qMRI [113]. Some clinical trials demonstrate the effectiveness of prescription patented crystalline GS (pCGS) as a symptomatic slow-acting drug for OA (SYSADOA) with a greater effect on pain than paracetamol and within the same range as oral NSAIDs [114]. The effect size for other glucosamine preparations has however been consistently approximated to zero [115]. In this regard, the ESCEO task force recommends prescription pCGS to be prescribed as a first-line SYSADOA for medium to long term symptom control in place of other glucosamine preparations [13]. Most other guidelines recommend against their use (Table 1).

Hyaluronic acid (HA) is found naturally in synovial fluid and is widely utilized therapeutically to treat OA [116]. The IA

Key points

- The current treatments mainly focus on reducing pain and other symptoms, as well as improving joint functional capacity. Along with a better understanding of pathological processes, some emerging disease-modifying therapies have been studied and hold promise for future OA management.
- In this narrative review, we will discuss current pharmacological treatments for OA patients, including traditional pharmacological treatments recommended by guidelines, as well as provide an update on recent developments of emerging medications with a focus on disease modifying OA drugs.

Key points

- Currently, most guidelines do not advocate for long-term use of opioids. The mechanism of action of opioids on OA is to inhibit the central nervous system pain pathway by binding the mu-opioid receptor. However, use of opioids is discouraged due to the serious side effects, such as:
- Nausea
- Vomiting
- Dizziness
- Drowsiness
- Constipation
- Headache
- Pain is the dominant symptom of OA and is the main reason people seek care and an important determinant of their ongoing management success. NSAIDs and other analgesics are widely used clinically to relieve pain. However, the avail- able drugs have side effects or toxicity profiles that are not suitable for long-term use.

injection of HA is purported to have symptomatic effects and may modify structure [117]. In general, most guidelines do not advocate for the use of hyaluronic acid as most studies have found it difficult to identify a clear distinction between the use of HA and intra-articular placebo (typically saline) and this has been recognized in limited recommendations for the therapy (Table 1). A number of trials have failed to find a major modifying effect of HA structure as compared to placebo [118,119]. It should be recognized that there is insufficient and poor evidence of a structure-modifying effect with these agents hence, more high-quality studies are needed to explore their positions as potential DMOADs in OA.

The popularity of IA administration has grown rapidly in recent years [120]. Compared to traditional oral drug administration, the IA route can minimize the systemic bioavailability and attendant side-effects [121]. Studies have shown IA treatments are more cost-effective in reducing the burden on elderly individuals with multiple debilitating diseases [122,123]. However, due to the rapid removal of therapeutic substances from the synovial space, the potential benefits of IA therapy for OA are not achievable by using currently available medicines and delivery vehicles. Sustained release systems are needed if the IA drug administration's potential is to be realized [124]. Recent clinical trials have also demonstrated a large placebo effect from IA administration, which increases the challenge to evaluate the efficacy in DMOAD trials [125].

Recently, studies find that placebo is also effective for OA. The placebo/contextual effect is attributable to an average 75% pain reduction, 71% functional improvement and 83% stiffness improvement in OA treatment [126]. This raises a question as to how, in clinical practice, to enhance the overall treatment effect of an OA intervention by improving the contextual effect, rather than extracting a specific treatment effect from the contextual effect as we typically do in clinical trials. Improving contextual factors such as patient–physician interaction or quality of care can achieve the enhancement. It would be very beneficial to further work on the creation of a basic contextual enhancement package that all physicians can provide on the basis of individual needs.

6. Expert opinion

OA is a chronic joint condition with numerous etiologies and different phenotypes. The osteoarthritic process is associated with structural abnormalities in articular cartilage, subchondral bone, synovial tissue, and other local tissues. Despite therapies and ongoing research that are currently available, there is still no 'cure' for OA. In today's clinical practice, physical and behavioral interventions, including exercise and weight loss remain the first-line therapies. In addition to alleviating pain and symptoms, the desired disease-modifying treatments should help rebuild normal cartilage structure and restore joint function. In view of the fact that OA is an entire joint condition rather than just articular cartilage, it is important to search for new therapeutic targets in changes in other tissues including subchondral bone remodeling or synovial inflammation. Traditional OA medications have been reported to be active in the management of pain and inflammation, but cannot reverse the OA cycle. Frequently occurring side effects conflict with their widespread use. Compared to traditional OA medications, new disease-modifying OA drugs that act by reducing inflammation, increasing cartilage repair, and inhibiting OA degeneration are associated with more pronounced effects and less side effects than traditional drugs. Most new drugs, however, are in the preclinical stage. Long-term RCTs are expected to improve the safety and efficacy of novel OA pharmacotherapy medicines.

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■ References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet (London, England). 2019 Apr 27;393(10182):1745–1759.
2. Jotanovic Z, Mihelic R, Sestan B, et al. Emerging pathways and promising agents with possible disease modifying effect in osteoarthritis treatment. Curr Drug Targets. 2014 June;15(6):635–661.
3. Felson DT. Clinical practice. Osteoarthritis of the knee. N Engl J Med. 2006 Feb 23;354(8):841–848.to
4. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evi dence-based, expert consensus guidelines. Osteoarthritis Cartilage. 2008 Feb;16(2):137–162.
5. Cohen E, Lee YC. A mechanism-based approach to the manage- ment of osteoarthritis pain. Curr Osteoporos Rep. 2015 Dec;13 (6):399–406.
6. Zhu Z, Li J, Ruan G, et al. Investigational drugs for the treatment of osteoarthritis, an update on recent developments. Expert Opin Investig Drugs. 2018 Nov;27(11):881–900. •• Key reference for the reader.
7. Wang K, Xu J, Hunter DJ, et al. Investigational drugs for the treatment of osteoarthritis. Expert Opin Investig Drugs. 2015;24 (12):1539–1556. •• Key reference for the reader.
8. Oo WM, Yu SP, Daniel MS, et al. Disease-modifying drugs in osteoarthri tis: current understanding and future therapeutics. Expert Opin Emerg Drugs. 2018 Dec;23(4):331–347. •• Key reference for the reader.
9. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019 Nov;27(11):1578–1589. • Updated OARSI guidelines for non-surgical management of knee OA in 2019.
10. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American college of rheumatology/arthritis foundation guideline for the management of os teoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2020;72(2):149–162. • Updated ACR guidelines for management of OA in 2020.
11. Management of osteoarthritis. 2019. Available from: http://path ways. nice.org.uk/pathways/osteoarthritis. Access date: 16 December, 2019.
12. Meiyappan KP, Cote MP, Bozic KJ, et al. Adherence to the American academy of orthopaedic surgeons clinical practice guidelines for nonop erative management of knee osteoarthritis. J Arthroplasty. 2020;35(2):347–352.
13. Bruyère O, Honvo G, Veronese N, et al. An updated algorithm recom mendation for the management of knee osteoarthritis from the Europe an society for clinical and economic aspects of osteo- porosis, osteoar thritis and musculoskeletal diseases (ESCEO). Semin Arthritis Rheum. 2019;49(3):337–350. • Updated ESCEOguidelines for management of knee OA in 2019.
14. Meneses SR, Goode AP, Nelson AE, et al. Clinical algorithms to aid osteoarthritis guideline dissemination. Osteoarthritis Cartilage. 2016 Sept;24(9):1487–1499. •• Key reference for the reader.
15. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical out- comes among overweight and obese adults with knee osteoar- thritis: the IDEA randomized clinical trial. JAMA. 2013;310 (12):1263–1273.
16. Roberts E, Delgado Nunes V, Buckner S, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. Ann Rheum Dis. 2016 Mar;75(3):552–559.
17. Leopoldino AO, Machado GC, Ferreira PH, et al. Paracetamol versus placebo for knee and hip osteoarthritis. Cochrane Database Syst Rev. 2019 Feb;25(2):CD013273.
18. Deveza LA, Hunter DJ, Van Spil WE. Too much opioid, too much harm. Osteoarthritis Cartilage. 2018 Mar;26(3):293–295.
19. Bjordal JM, Ljunggren AE, Klovning A, et al. Non-steroidal anti-inflam matory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. BMJ. 2004;329(7478):1317. •• Key reference for the reader.
20. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthr Cartil. 2010;18(4):476–499.
21. Tieppo Francio V, Davani S, Towery C, et al. Oral versus topical diclofenac sodium in the treatment of osteoarthritis. J Pain Palliat Care Pharmacother. 2017 June;31(2):113–120.
22. Kienzler J-L, Gold M, Nollevaux F. Systemic bioavailability of topical di clofenac sodium gel 1% versus oral diclofenac sodium in healthy volun teers. J Clin Pharmacol. 2010;50(1):50–61.
23. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329(7456):15–19.
24. Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Arthritis Res Ther. 2013;15(Suppl 3):S3.
25. Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarc- tion with NSAIDs in real world use: Bayesian meta-analysis of individual patient data. BMJ. 2017;357:j1909.
26. Al-Saeed A. Gastrointestinal and Cardiovascular risk of nonsteroidal an ti-inflammatory drugs. Oman Med J. 2011;26(6):385–391.
27. Conaghan PG, Arden N, Avouac B, et al. Safety of paracetamol in osteo arthritis: what does the literature say? Drugs Aging. 2019;36 (Suppl 1):7–14.
28. Graham GG, Scott KF. Mechanism of action of paracetamol. Am J Ther. 2005;12(1):46–55.
29. Towheed TE, Maxwell L, Judd MG, et al. Acetaminophen for osteoar thritis. Cochrane Database Syst Rev. 2006;1:CD004257.
30. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain–United States, 2016. JAMA. 2016;315 (15):1624–1645.
31. O'Neil CK, Hanlon JT, Marcum ZA. Adverse effects of analgesics com monly used by older adults with osteoarthritis: focus on non-opioid and opioid analgesics. Am J Geriatr Pharmacother. 2012;10(6):331–342.
32. Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for os teoarthritis: a meta-analysis of randomized controlled trials. Osteoarthr Cartil. 2007;15(8):957–965.
33. Volkow ND, McLellan AT. Opioid abuse in chronic pain–misconcep- tions and mitigation strategies. N Engl J Med. 2016;374 (13):1253–1263.
34. Miller RE, Miller RJ, Malfait AM. Osteoarthritis joint pain: the cyto- kine connection. Cytokine. 2014 Dec;70(2):185–193.
35. Malfait AM, Schnitzer TJ. Towards a mechanism-based approach to pain management in osteoarthritis. Nat Rev Rheumatol. 2013 Nov;9(11):654–664.
36. Smelter E, Hochberg MC. New treatments for osteoarthritis. Curr Opin Rheumatol. 2013 May;25(3):310–316.
37. Denk F, Bennett DL, McMahon SB. Nerve growth factor and pain mech anisms. Annu Rev Neurosci. 2017 July 25;40:307–325.
38. Mantyh PW, Koltzenburg M, Mendell LM, et al. Antagonism of nerve growth factor-TrkA signaling and the relief of pain. Anesthesiology. 2011 July;115(1):189–204.
39. Lane NE, Schnitzer TJ, Birbara CA, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. N Engl J Med. 2010 Oct 14;363(16):1521–1531. •• The first large RCT of tanezumab for knee OA pain an revealed dra matic pain relief in treatment group.
40. Chen J, Li J, Li R, et al. Efficacy and safety of tanezumab on osteoarthritis knee and hip pains: a meta-analysis of randomized controlled trials. Pain Med (Malden, Mass). 2017 Feb 01;18(2):374–385.
41. Schnitzer TJ, Easton R, Pang S, et al. Effect of tanezumab on joint pain, physical function, and patient global assessment of osteoar thritis among patients with osteoarthritis of the hip or knee: a randomized clinical trial. JAMA. 2019 July 02;322(1):37–48.
42. Mullard A. Drug developers reboot anti-NGF pain programmes. Nat Rev Drug Discov. 2015 May;14(5):297–298.
43. Hochberg MC. Serious joint-related adverse events in randomized controlled trials of anti-nerve growth factor monoclonal antibodies. Osteoarthr Cartil. 2015 Jan;23(Suppl 1):S18–21.
44. Lane NE, Corr M. Osteoarthritis in 2016: anti-NGF treatments for pain - two steps forward, one step back? Nat Rev Rheumatol. 2017 Jan 25;13(2):76–78.
45. Hochberg MC, Tive LA, Abramson SB, et al. When is osteonecrosis not osteonecrosis? Adjudication of reported serious adverse joint events in the tanezumab clinical development program. Arthritis & Rheumatology (Hoboken, N.J.) 2016 Feb;68(2):382–391.
46. Losina E, Michl G, Collins JE, et al. Model-based evaluation of cost-effec tiveness of nerve growth factor inhibitors in knee osteoarthritis: impact of drug cost, toxicity, and means of administration. Osteoarthr Cartil. 2016 May;24(5):776–785.
47. Davidson D, Blanc A, Filion D, et al. Fibroblast growth factor

(FGF) 18 signals through FGF receptor 3 to promote chondrogenesis. J Biol Chem. 2005 May 27;280(21):20509–20515.
48. Ellsworth JL, Berry J, Bukowski T, et al. Fibroblast growth factor-18 is a trophic factor for mature chondrocytes and their progenitors. Osteoar thr Cartil. 2002 Apr;10(4):308–320.
49. Lohmander LS, Hellot S, Dreher D, et al. Intraarticular sprifermin (recombinant human fibroblast growth factor 18) in knee osteoar- thritis: a randomized, double-blind, placebo-controlled trial. Arthritis & Rheumatology (Hoboken, N.J.). 2014 July;66 (7):1820–1831.
50. Roemer FW, Aydemir A, Lohmander S, et al. Structural effects of sprifer min in knee osteoarthritis: a post-hoc analysis on cartilage and non-car tilaginous tissue alterations in a randomized controlled trial. BMC Mus culoskelet Disord. 2016 July 09;17:267.
51. Eckstein F, Wirth W, Guermazi A, et al. Brief report: intraarticular spri fermin not only increases cartilage thickness, but also reduces cartilage loss: location-independent post hoc analysis using magnetic resonance imaging. Arthritis & Rheumatology (Hoboken, N.J.). 2015 Nov;67(11):2916–2922.
52. Gühring H, Kraines J, Moreau F, et al. Op0010 cartilage thickness modification with sprifermin in knee osteoarthritis patients translates into symptomatic improvement over placebo in patients at risk of fur ther structural and symptomatic progression: post-hoc analysis of the phase ii forward trial. Ann Rheum Dis. 2019;78(Suppl2):70–71.
53. Dahlberg LE, Aydemir A, Muurahainen N, et al. A first-in-human, dou ble-blind, randomised, placebo-controlled, dose ascending study of in tra-articular rhFGF18 (sprifermin) in patients with advanced knee osteo arthritis. Clin Exp Rheumatol. 2016;34 (3):445–450. • A first-in-human RCT to assess the safety of intra-articular rhFGF18 (sprifermin) in pa tients with advanced knee OA.
54. Hochberg MC, Guermazi A, Guehring H, et al. Effect of intra-articular sprifermin vs placebo on femorotibial joint cartilage thickness in patients with osteoarthritis: the forward randomized clinical trial. JAMA. 2019 oct 08;322(14):1360–1370.
55. Madry H, Cucchiarini M. Gene therapy for human osteoarthritis: princi ples and clinical translation. Expert Opin Biol Ther. 2016;16 (3):331–346.
56. Ha CW, Noh MJ, Choi KB, et al. Initial phase I safety of retrovirally transduced human chondrocytes expressing transforming growth factor-beta-1 in degenerative arthritis patients. Cytotherapy. 2012 Feb;14(2):247–256.
57. Lee MC, Ha CW, Elmallah RK, et al. A placebo-controlled rando- mised trial to assess the effect of TGF-ß1-expressing chondrocytes in patients with arthritis of the knee. Bone Joint J. 2015 July;97-b (7):924–932.
58. Ha CW, Cho JJ, Elmallah RK, et al. A multicenter, single-blind, phase iia clinical trial to evaluate the efficacy and safety of a cell-mediated gene therapy in degenerative knee arthritis patients. Hum Gene Ther Clin Dev. 2015 June;26(2):125–130.
59. Kim MK, Ha CW, In Y, et al. A multicenter, double-blind, phase iii clini cal trial to evaluate the efficacy and safety of a cell and gene therapy in knee osteoarthritis patients. Hum Gene Ther Clin Dev. 2018 Mar;29(1):48–59.
60. Wang Y, Fan X, Xing L, et al. Wnt signaling: a promising target for osteoarthritis therapy. Cell Commun Signal. 2019 Aug 16;17(1):97.
61. Yazici Y, McAlindon TE, Fleischmann R, et al. A novel Wnt pathway inhibitor, SM04690, for the treatment of moderate to severe osteoar thritis of the knee: results of a 24-week, randomized, controlled, phase 1 study. Osteoarthr Cartil. 2017 Oct;25(10):1598–1606.
62. Li NG, Shi ZH, Tang YP, et al. New hope for the treatment of osteoar thritis through selective inhibition of MMP-13. Curr Med Chem. 2011;18:7.
63. Hui W, Litherland GJ, Elias MS, et al. Leptin produced by joint white adipose tissue induces cartilage degradation via upregulation and activation of matrix metalloproteinases. Ann Rheum Dis. 2012;71 (3):455–462.
64. Liu J, Khalil RA. Matrix metalloproteinase inhibitors as investigational and therapeutic tools in unrestrained tissue remodeling and pathologi cal disorders. Prog Mol Biol Transl Sci. 2017;148:355–420.
65. Wang M, Sampson ER, Jin H, et al. MMP13 is a critical target gene during the progression of osteoarthritis. Arthritis Res Ther. 2013;15 (1):R5.
66. Kalva S, Saranyah K, Suganya PR, et al. Potent inhibitors precise to S1□ loop of MMP-13, a crucial target for osteoarthritis. J Mol Graph Model. 2013;44:297–310.
67. Piecha D, Weik J, Kheil H, et al. Novel selective MMP-13 inhibitors re duce collagen degradation in bovine articular and human osteoarthritis cartilage explants. Inflamm Res. 2010;59 (5):379–389.
68. Schnute ME, O'Brien PM, Nahra J, et al. Discovery of (pyridin-4-yl)- 2H-tetrazole as a novel scaffold to identify highly selective matrix metalloproteinase-13 inhibitors for the treatment of osteoarthritis. Bioorg Med Chem Lett. 2010;20(2):576–580.
69. Yang CY, Chanalaris A, Troeberg L. ADAMTS and ADAM metallopro teinases in osteoarthritis - looking beyond the 'usual suspects'. Osteoar thr Cartil. 2017;25(7):1000–1009.
70. Verma P, Dalal K. ADAMTS-4 and ADAMTS-5: key enzymes in osteoar thritis. J Cell Biochem. 2011;112(12):3507–3514.
71. Chockalingam PS, Sun W, Rivera-Bermudez MA, et al. Elevated aggre canase activity in a rat model of joint injury is attenuated by an aggreca nase specific inhibitor. Osteoarthr Cartil. 2011;19 (3):315–323.
72. Siebuhr A, Bay-Jensen A-C, Thudium C, et al. The anti-ADAMTS-5 nanobody®, M6495, protects against cartilage breakdown in carti- lage and synovial joint tissue explant models. Osteoarthr Cartil. 2018;26:S187.
73. Childs BG, Gluscevic M, Baker DJ, et al. Senescent cells: an emer- ging target for diseases of ageing. Nat Rev Drug Discov. 2017;16 (10):718–735.
74. Baker DJ, Wijshake T, Tchkonia T, et al. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature. 2011;479(7372):232–236.
75. Baker DJ, Childs BG, Durik M, et al. Naturally occurring p16 (Ink4a)-pos itive cells shorten healthy lifespan. Nature. 2016;530 (7589):184–189.
76. Jeon OH, Kim C, Laberge R-M, et al. Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nat Med. 2017;23 (6):775–781.
77. Osborne H, Castricum A. Change to Australasian college of sport and exercise physicians-position statement: the place of mesenchymal stem/stromal cell therapies in sport and exercise medicine. Br J Sports Med. 2016;50(20):1229.
78. Cui G-H, Wang YY, Li C-J, et al. Efficacy of mesenchymal stem cells in treating patients with osteoarthritis of the knee: a meta-analysis. Exp Ther Med. 2016;12(5):3390–3400.
79. Pas HI, Winters M, Haisma HJ, et al. Stem cell injections in knee osteo arthritis: a systematic review of the literature. Br J Sports Med. 2017;51(15):1125–1133.
80. Yubo M, Yanyan L, Li L, et al. Clinical efficacy and safety of mesenchy mal stem cell transplantation for osteoarthritis treatment: a meta-analy sis. PLoS ONE. 2017;12(4):e0175449.
81. Vangsness CT, Farr J, Boyd J, et al. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, con-trolled study. J Bone Joint Surg Am. 2014;96(2):90–98.
82. Xing D, Wang Q, Yang Z, et al. Mesenchymal stem cells injections or knee osteoarthritis: a systematic overview. Rheumatol Int. 2018;38(8):1399–1411.
83. Palm-Espling ME, Wittung-Stafshede P. Reaction of platinum anticancer drugs and drug derivatives with a copper transporting protein, Atox1. Biochem Pharmacol. 2012;83(7):874–881.
84. Neogi T, Li S, Peloquin C, et al. Effect of bisphosphonates on knee re placement surgery. Ann Rheum Dis. 2018;77(1):92–97.
85. Fu S-H, Wang C-Y, Yang R-S, et al. Bisphosphonate use and the risk of undergoing total knee arthroplasty in osteoporotic patients with osteoarthritis: a nationwide cohort study in Taiwan. J Bone Joint Surg Am. 2017;99(11):938–946.
86. Vaysbrot EE, Osani MC, Musetti MC, et al. Are bisphosphonates efficacious in knee osteoarthritis? A meta-analysis of randomized controlled trials. Osteoarthr Cartil. 2018;26(2):154–164.
87. Manoy P, Yuktanandana P, Tanavalee A, et al. Vitamin D supplementation improves quality of life and physical perfor- mance in osteoarthritis patients. Nutrients. 2017;9(8):799.
88. Gao X-R, Chen Y-S DW. The effect of vitamin D supplementation on knee osteoarthritis: a meta-analysis of randomized controlled trials. Int J Surg. 2017;46:14–20.
89. Bassiouni H, Aly H, Zaky K, et al. Probing the relation between vitamin d deficiency and progression of medial femoro-tibial osteoarthritis of the knee. Curr Rheumatol Rev. 2017;13 (1):65–71.
90. Hussain SM, Daly RM, Wang Y, et al. Association between serum concentration of 25-hydroxyvitamin D and the risk of hip arthro- plasty for osteoarthritis: result from a prospective cohort study. Osteo arthr Cartil. 2015;23(12):2134–2140.
91. Wang X, Cicuttini F, Jin X, et al. Knee effusion-synovitis volume measurement and effects of vitamin D supplementation in patients with knee osteoarthritis. Osteoarthr Cartil. 2017;25 (8):1304–1312.
92. Thomas S, Browne H, Mobasheri A, et al. What is the evidence for

a role for diet and nutrition in osteoarthritis? Rheumatology (Oxford, England). 2018;57(suppl_4): iv61–iv74.
93. Edwards RR, Cahalan C, Calahan C, et al. Pain, catastrophizing, and depression in the rheumatic diseases. Nat Rev Rheumatol. 2011;7 (4):216–224.
94. Murakami S, Lefebvre V, de Crombrugghe B. Potent inhibition of the master chondrogenic factor Sox9 gene by interleukin-1 and tumor necrosis factor-alpha. J Biol Chem. 2000;275 (5):3687–3692.
95. Cohen SB, Proudman S, Kivitz AJ, et al. A randomized, double-blind study of AMG 108 (a fully human monoclonal antibody to IL-1R1) in patients with osteoarthritis of the knee. Arthritis Res Ther. 2011;13 (4):R125.
96. Jrvinen K, Vuolteenaho K, Nieminen R, et al. Selective iNOS inhibitor 1400W enhances anti-catabolic IL-10 and reduces destructive MMP-10 in OA cartilage. Survey of the effects of 1400W on inflammatory mediators produced by OA cartilage as detected by protein antibody array. Clin Exp Rheumatol. 2008;26(2):275–282.
97. Hellio le Graverand M-P, Clemmer RS, Redifer P, et al. A 2-year randomised, double-blind, placebo-controlled, multicentre study of oral selective iNOS inhibitor, cindunistat (SD-6010), in patients with symptomatic osteoarthritis of the knee. Ann Rheum Dis. 2013;72 (2):187–195. • A multi-centre RCT to assess therapeutic effects of oral selec- tive iNOS inhitor in patients with symptomatic knee OA.
98. Hellio Le Graverand M-P, Clemmer RS, Brunell RM, et al. Considerations when designing a disease-modifying osteoarthritis drug (DMOAD) trial using radiography. Semin Arthritis Rheum. 2013;43(1):1–8.
99. Karsdal MA, Bay-Jensen AC, Lories RJ, et al. The coupling of bone and cartilage turnover in osteoarthritis: opportunities for bone antiresorptives and anabolics as potential treatments? Ann Rheum Dis. 2014;73(2):336–348.
100. Tenti S, Cheleschi S, Guidelli GM, et al. What about strontium ranelate in osteoarthritis? Doubts and securities. Mod Rheumatol. 2014;24(6):881–884.
101. Reginster JY. Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind randomised, placebo-controlled trial. Ann Rheum Dis. 2014;73(2):e8.
102. Han W, Fan S, Bai X, et al. Strontium ranelate, a promising disease modifying osteoarthritis drug. Expert Opin Investig Drugs. 2017;26 (3):375–380. • This paper showed that strontium ranelate could be a promising DMOAD for OA patients of bone phenotypes.
103. Hunter DJ, Nevitt M, Losina E, et al. Biomarkers for osteoarthritis: current position and steps towards further validation. Best Pract Res Clin Rheumatol. 2014 Feb;28(1):61–71.
104. Peterfy CG, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthr Cartil. 2008 Dec;16 (12):1433–1441.
105. Osteoarthritis: A Serious Disease SttUSFaDA. [Cited 2016 Dec 1]. Available from: https://www.oarsi.org/education/oarsi-resources /oarsi-white-paper-oa-serious-disease
106. Kraus VB, Simon LS, Katz JN, et al. Proposed study designs for approval based on a surrogate endpoint and a post-marketing confir matory study under FDA's accelerated approval regulations for disease modifying osteoarthritis drugs. Osteoarthr Cartil. 2019 Apr;27(4):571–579.
107. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskelet Disord. 2008;9:116.
108. Mills K, Hübscher M, O'Leary H, et al. Current concepts in joint pain in knee osteoarthritis. Schmerz. 2019;33(1):22–29.
109. Vlad SC, LaValley MP, McAlindon TE, et al. Glucosamine for pain in osteoarthritis: why do trial results differ? Arthritis Rheum. 2007;56 (7):2267–2277.
110. Pavelká K, Gatterová J, Olejarová M, et al. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med. 2002;162(18):2113–2123.
111. Wildi LM, Raynauld J-P, Martel-Pelletier J, et al. Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. Ann Rheum Dis. 2011;70(6):982–989.
112. Kahan A, Uebelhart D, De Vathaire F, et al. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2009;60 (2):524–533.
113. Martel-Pelletier J, Roubille C, Abram F, et al. First-line analysis of the effects of treatment on progression of structural changes in knee osteoarthritis over 24 months: data from the osteoarthritis initiative progression cohort. Ann Rheum Dis. 2015;74(3):547–556.
114. Bruyère O, Altman RD, Reginster J-Y. Efficacy and safety of glucosamine sulfate in the management of osteoarthritis: evidence from real-life setting trials and surveys. Semin Arthritis Rheum. 2016;45(4 Suppl):S12–S17.
115. Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev. 2005;2: CD002946.
116. Faust HJ, Sommerfeld SD, Rathod S, et al. A hyaluronic acid binding peptide-polymer system for treating osteoarthritis. Biomaterials. 2018;183:93–101.
117. 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). Ann Rheum Dis. 2003;62(12):1145–1155.
118. Wang Y, Hall S, Hanna F, et al. Effects of hylan G-F 20 supplementation on cartilage preservation detected by magnetic resonance imaging in osteoarthritis of the knee: a two-year single-blind clinical trial. BMC Musculoskelet Disord. 2011;12:195.
119. Pham T, Le Henanff A, Ravaud P, et al. Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised con trolled study in symptomatic knee osteoarthritis. Ann Rheum Dis. 2004;63(12):1611–1617.
120. Roman-Blas JA, Bizzi E, Largo R, et al. An update on the up and coming therapies to treat osteoarthritis, a multifaceted disease. Expert Opin Pharmacother. 2016;17(13):1745–1756.
121. Nguyen C, Rannou F. The safety of intra-articular injections for the treatment of knee osteoarthritis: a critical narrative review. Expert Opin Drug Saf. 2017;16(8):897–902.
122. Rosen J, Sancheti P, Fierlinger A, et al. Cost-effectiveness of different forms of intra-articular injections for the treatment of osteoarthritis of the knee. Adv Ther. 2016;33:6.
123. Wehling P, Evans C, Wehling J, et al. Effectiveness of intra-articular therapies in osteoarthritis: a literature review. Ther Adv Musculoskelet Dis. 2017;9(8):183–196.
124. Edwards SH. Intra-articular drug delivery: the challenge to extend drug residence time within the joint. Vet J. 2011 Oct;190(1):15–21.
125. Karsdal MA, Michaelis M, Ladel C, et al. Disease-modifying treatments for osteoarthritis (DMOADs) of the knee and hip: lessons learned from failures and opportunities for the future. Osteoarthr Cartil. 2016;24(12):2013–2021.
126. Zhang W. The powerful placebo effect in osteoarthritis. Clin Exp Rheumatol. 2019;37(Suppl 120):118–123.