CLINICAL PRACTICE

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Osteoarthritis of the Knee

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 60-year-old woman presents with pain in both knees that had started gradually several months earlier. The pain is dull, is not localized to one part of the knee, does not radiate, worsens with some heavy activity, and abates with rest. She reports having no redness, swelling, or morning stiffness, but she has stiffness in the knee after inactivity during the day. She reports that she has not had a knee injury or instances of the knee giving way or locking. She was previously overweight and worries that the pain will make it difficult to maintain a healthy weight and to hike, a favorite activity. Examination reveals no warmth or swelling, mild crepitus, and a normal range of motion. How should the patient be evaluated and treated?

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THE CLINICAL PROBLEM

Osteoarthritis of the knee is common, affecting 37% of persons 60 years of age or older who participated in the National Health and Nutrition Examination Survey (based on radiographic examination),[1] and is more common in women than in men.[2] The prevalence of osteoarthritis is expected to increase with the aging of the U.S. population.[3]

Osteoarthritis represents failed repair of joint damage resulting from stresses initiated by any joint or periarticular tissue abnormality. Although cartilage loss is fundamental, osteoarthritis is a disease of the whole joint (Fig. 1). The rate of progression varies among persons and within a knee over time. The symptoms and signs of knee osteoarthritis include pain, stiffness, reduced joint motion, and muscle weakness. Long-term consequences can include reduced physical activity, deconditioning, impaired sleep, fatigue, depression, and disability. Symptom severity and structural damage on imaging are often discordant. In early osteoarthritis, this discordance may reflect insensitivity of radiography; in persons at high risk for knee osteoarthritis and with normal radiographs, magnetic resonance imaging (MRI) may reveal disease manifestations.[4,5] As disease advances, the discrepancy may relate to pain sensitization (abnormal responsiveness from changes in nociceptive processing in the peripheral or central nervous system), adaptation to chronic pain, or reduction in activity to avoid pain.

Factors that have been associated with an increased risk of knee osteoarthritis include older age, female sex, overweight or obesity, knee injury, occupational factors (e.g., knee bending, heavy lifting, and squatting), and varus or valgus alignment. Risk is not increased with recreational physical activity.[6,7]

Pain from osteoarthritis of the knee is difficult to study longitudinally because it fluctuates and its pattern evolves. Episodic pain is predictable in early stages but becomes less predictable and more distressing in late stages.[8] Factors that have

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KEY CLINICAL POINTS

OSTEOARTHRITIS OF THE KNEE

- Potential long-term consequences of knee osteoarthritis include reduced physical activity, deconditioning, impaired sleep, fatigue, depression, functional decline, and disability.
- There is often a discrepancy between the severity of symptoms and the severity of knee osteoarthritis as assessed on radiography; such discrepancies may relate to pain sensitization, adaptation to chronic pain, or reduction in activity to avoid pain.
- Core treatments for knee osteoarthritis include education, physical activity including exercise (strengthening, aerobic, or neuromuscular exercises or mind–body exercise such as tai chi), and weight management.
- Topical nonsteroidal antiinflammatory drugs (NSAIDs) are a first-line treatment for knee osteoarthritis, given evidence of benefit similar to that with oral NSAIDs but with fewer adverse effects.
- If topical treatment is inadequate or not feasible, treatment often involves either an oral NSAID plus a proton-pump inhibitor or a cyclooxygenase-2 (COX-2) inhibitor; however, therapy should be tailored according to the presence of gastrointestinal or cardiovascular coexisting conditions or widespread pain.

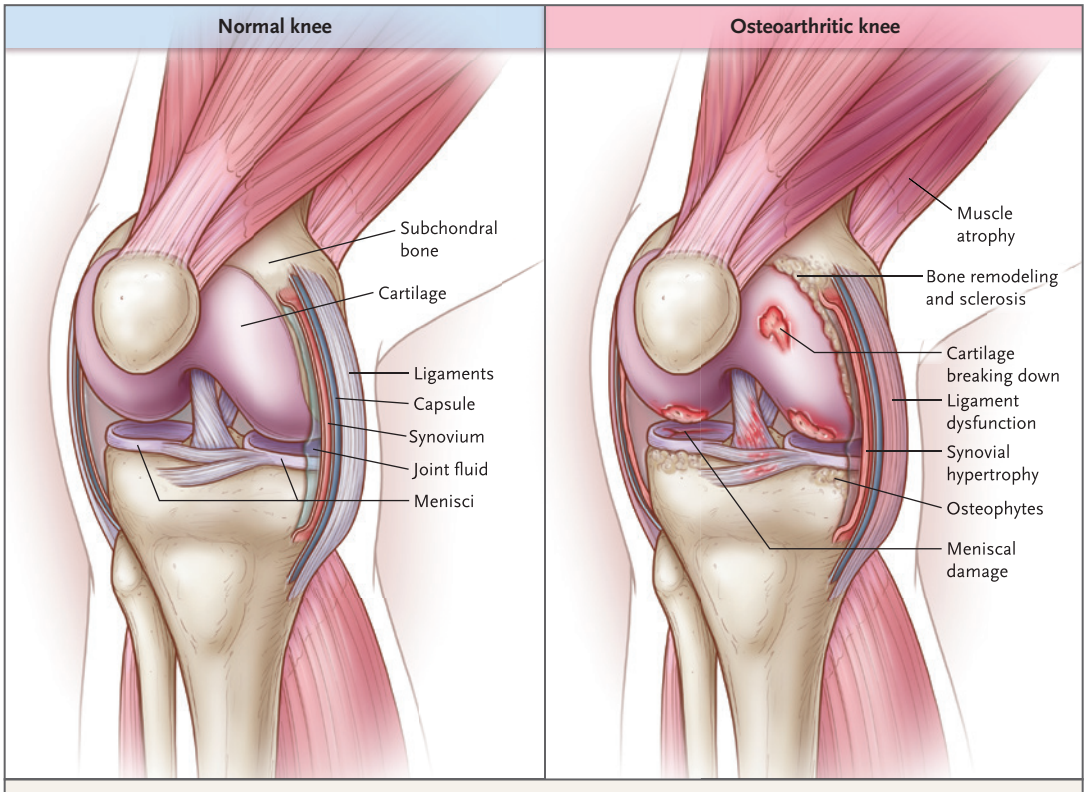

Figure 1. Comparison of Normal Knee and Osteoarthritic Knee.

Differences between a normal knee and an osteoarthritic knee with regard to the involvement of articular and periarticular tissues are shown.

been associated with pain in longitudinal studies include younger age, female sex, non-White race, lower educational level, obesity, burden of coexisting conditions, psychological factors (e.g., depression, low level of self-efficacy [belief in one's capacities to mobilize internal resources and actions needed to meet situational demands], and pain catastrophizing [tendency to magnify sensations and feel helpless]), and pain sensitization.[9,10] With the exception of younger age, these factors are also risk factors for functional impairment, a precursor of disability; additional

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risk factors include older age, falls, malalignment, disease severity, and knee instability, whereas greater physical activity, strength, self-efficacy, and social support are associated with reduced risk.[11]

STRATEGIES AND EVIDENCE

EVALUATION

A medical history and physical examination are typically sufficient to establish the diagnosis of osteoarthritis. One or both knees may be affected, with or without more generalized osteoarthritis (defined as the involvement of the hand and at least one large joint). Symptoms begin gradually, usually in men in their 40s or older and in women in perimenopause or older. The pain is often dull, involving the whole knee or more localized, increases with joint use, and abates with rest. As disease advances, pain may occur at rest and at night, interfering with sleep. Morning stiffness lasts less than 30 minutes, and stiffness occurs briefly after daytime inactivity.

Findings of knee osteoarthritis include crepitus, bony enlargement, reduced knee flexion, flexion contracture, and tenderness. Erythema, warmth, and swelling, if present, are mild. More marked inflammation suggests another process (e.g., acute septic or crystal-related arthritis or chronic inflammatory arthritis). Other joints should be examined, including the hip to rule out osteoarthritis at that site. Inspection of standing alignment and gait may reveal fixed or dynamic malalignment and instability. Radiography of the knee (to visualize the tibiofemoral [weight-bearing posteroanterior view] and patellofemoral [lateral or skyline view] compartments) may confirm osteoarthritis-related changes, such as osteophytes, subchondral sclerosis, cysts, bone attrition, and asymmetric joint-space narrowing (which may be worse in the medial or lateral tibiofemoral or patellofemoral compartment or which may involve a combination of the tibiofemoral and patellofemoral compartments), and aid in the assessment of disease stage, which informs expectations of the course of disease (Fig. 2). MRI is indicated only in rare circumstances (e.g., if there are persistent mechanical symptoms and objective locking, which would possibly indicate a displaced meniscal tear).

There are no blood or urine tests to diagnose osteoarthritis. Joint aspiration is not indicated routinely, and fluid may be unobtainable from many osteoarthritic knees. However, aspiration may be indicated in selected patients to distinguish osteoarthritis (typical white-cell count, <2000 per cubic millimeter) from other arthritides. Conditions that may manifest with chronic knee pain are summarized in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

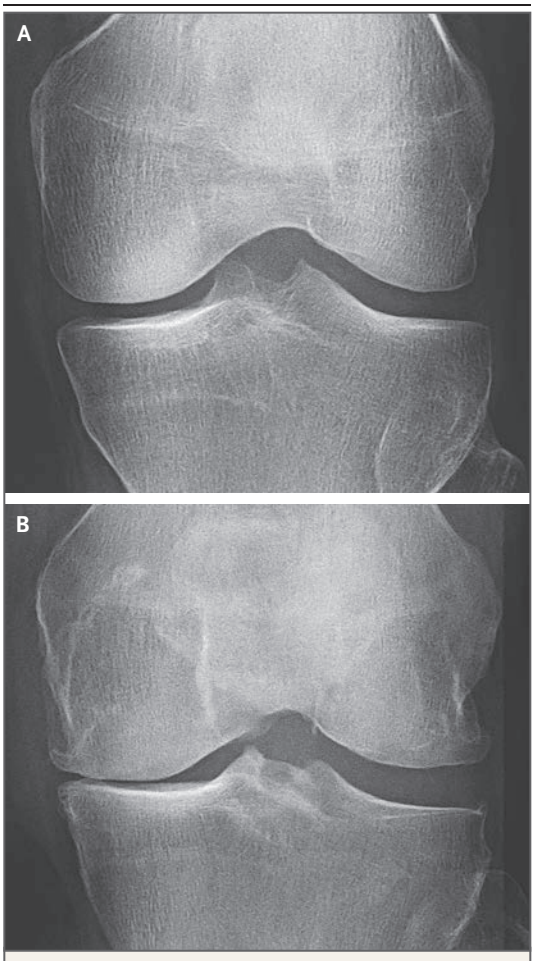

Figure 2. Radiographs of Normal Knee and Osteoarthritic Knee.

Panel A shows a normal knee, without osteophytes or joint-space narrowing. Panel B shows moderate-to-severe joint-space narrowing of the medial tibiofemoral compartment and subchondral sclerosis of the medial tibia. This radiograph shows definite marginal osteophytes at the medial tibia and femur and the lateral femur.

TREATMENT

In recent years, there has been a shift from primarily pharmacologic therapy to nonpharmaco-

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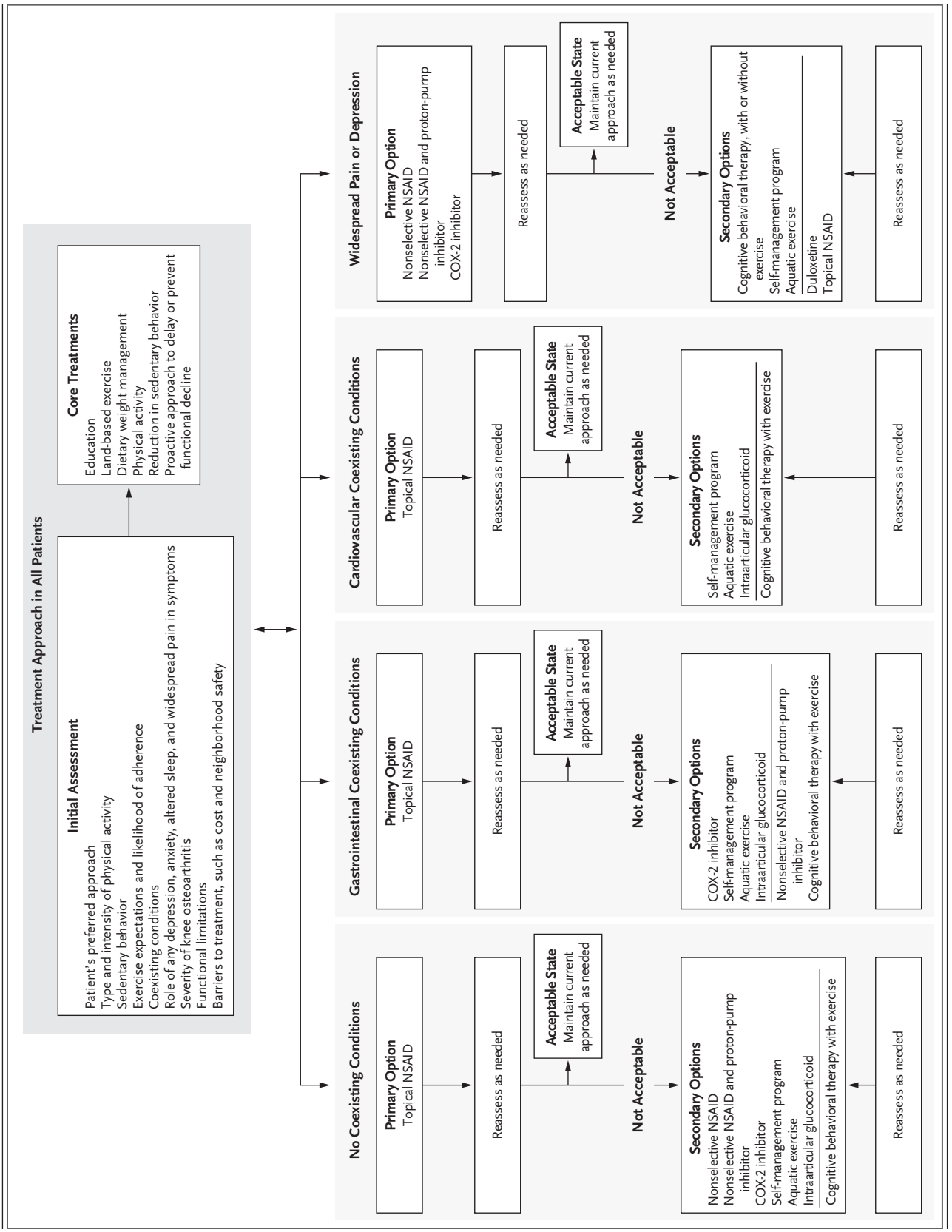

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Figure 3 (facing page). Treatment Algorithm for Knee Osteoarthritis.

Adapted from Bannuru et al.[12] Shown are treatment approaches in all patients and approaches in patients with various coexisting conditions. The presence of coexisting conditions is determined on the basis of the initial assessment and reassessments. An acceptable state on reassessment means that the patient and clinician agree that the current state is acceptable on the basis of symptom assessment, examination, and assessment of side effects of treatment; changes in condition should be documented. If the patient and clinician deem that the condition is not acceptable, it is important to approximate the patient's adherence to and the effectiveness of the current treatment approach and to then address barriers to adherence, adjust the dose, or modify the approach. Primary options are based on recommendation levels 1A or 1B; secondary options above the line are based on recommendation levels 1A or 1B, and those below the line on recommendation level 2.[12] COX-2 denotes cyclooxygenase-2, and NSAID nonsteroidal antiinflammatory drug.

logic therapy, owing to the limited benefits of the former and evidence that nonpharmacologic approaches are more likely to relieve symptoms in the long term and to delay or prevent functional decline. The treatment of knee osteoarthritis is multimodal and should incorporate the initial assessment variables shown in Figure 3. Patients ought to be educated regarding the variability in natural history, the value of strength training in protecting joints, injury prevention, the role of coping skills and self-efficacy, and the importance of a proactive approach to prevent functional decline.

NONPHARMACOLOGIC THERAPY

Exercise and Diet

Exercise is an essential component of the management of knee osteoarthritis.[12-15] A systematic review of randomized trials of land-based therapeutic exercise (vs. varied comparators) in persons with knee osteoarthritis showed that exercise significantly reduced pain (with a moderate effect size based on high-quality evidence from 44 trials) and improved physical function (with a moderate effect size based on moderate-quality evidence from 44 trials) and quality of life (with a small effect size based on high-quality evidence from 13 trials).[14] Pain and function benefits were sustained at least 2 to 6 months after the end of formal treatment.[14] Contrary to potential concerns that exercise might pose long-term risks, a systematic review of studies of low-impact exercise in older adults with knee pain or osteoarthritis showed no increase in pain and no progression of disease on imaging at the group level.[16]

Exercise goals include maintaining or improving aerobic fitness, range of motion, and strength and reducing the risk of falls. Studies showing benefit have involved aerobic exercise (e.g., treadmill, track, or community-based walking), strengthening (isokinetic, isometric, or elastic-band exercises), neuromuscular exercise, aquatic activities, balance exercise, and mind–body exercise. Neuromuscular exercise focuses on reducing weakness and improving sensorimotor control and functional stability by means of progressive performance exercises. Aquatic settings enable concomitant low-impact aerobic, strengthening, and range-of-motion exercises but are less accessible than land-based exercise options. Balance exercises are beneficial in the treatment of functional instability or for addressing higher fall risk. In a randomized, single-blind trial comparing tai chi with physical therapy, tai chi led to similar improvements as seen with physical therapy according to a validated osteoarthritis index at 12 weeks and greater improvements in depression and the physical component of quality of life.[17]

Exercise therapy is, ideally, initiated and personalized by a physical therapist, who can consider the patient's preferences, outcome expectations, pain severity, sensitivity to exercise, self-efficacy, and fear of movement in establishing goals and progression. Effective multimodal therapy can be delivered remotely. In patients with knee osteoarthritis, Internet-delivered educational material and a patient-completed program of skills training for coping with pain[18] with therapist-prescribed exercises administered by means of Skype led to a greater reduction in pain and improvement in function than educational material alone; the benefit was sustained for at least 6 months[19] and was consistent across ages and educational levels.[20]

Guidelines emphasize the importance of maintaining physical activity and limiting sedentary behavior for joint and overall health in persons with knee osteoarthritis,[12,13,21] but how to achieve this is unclear. In the observational Osteoarthritis Initiative, fewer than 11% of persons with knee osteoarthritis met the Department of Health and Human Services guideline of moderate-to-

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vigorous activity 150 minutes per week.[22] Observational data indicate that lower levels of activity may be beneficial. Greater time spent daily in light-intensity activities was associated with less incident and progressive disability.[23] One hour per week of moderate-to-vigorous activity[24] was associated with a greater likelihood of remaining free of disability than activity lasting less than 1 hour per week.

In persons with knee osteoarthritis who are overweight or obese, weight loss is strongly recommended.[12,13] In a randomized trial comparing diet with exercise or both in overweight and obese persons with knee osteoarthritis, the combined intervention resulted in greater weight loss, less pain, and better function than either intervention alone[25]; a secondary analysis showed significant associations between the amount of weight loss and assessments of pain, function, and distance walked in 6 minutes.[26] A meta-analysis of nine trials showed a moderate reduction in pain with combined diet and exercise but not with diet alone.[27] In addition, an observational study involving persons who were overweight or obese who either had knee osteoarthritis or were at high risk for knee osteoarthritis showed that weight loss over a period of 4 years was associated with slowed degeneration of the knee cartilage, as assessed with the use of compositional MRI.[28]

Self-Efficacy and Self-Management Programs and Pain-Coping Skills Training

Self-efficacy and self-management programs, which can be delivered remotely, include education; setting goals and contracts; practice; graduated behavioral interventions to promote ability to manage pain, fear, stress, depression, anxiety, exercise, weight, and joint protection; and patient's self-monitoring. Meta-analyses of such programs have shown small-to-moderate effect sizes regarding improvements in self-efficacy in patients with knee osteoarthritis[29] or musculoskeletal conditions.[30] Pain-coping skills training often targets catastrophizing, which can intensify movement avoidance[31] and reduce engagement in health-promoting behaviors.[32] A meta-analysis of psychological interventions for pain management, which included 23 trials of pain-coping skills training, showed reductions in pain and improvements in function in patients with osteoarthritis or rheumatoid arthritis.[33] Randomized trials have also shown benefits of pain-coping skills training in patients with painful knee osteoarthritis.[34,35]

Other Nonpharmacologic Interventions

Owing to insufficient benefit and data quality, guidelines recommend against massage therapy, manual therapy (manual traction, mobilization or manipulation, or passive range of motion), and wedge insoles.[12,13] Study results are inconsistent regarding the benefit of thermal interventions (locally applied heat or cold) and acupuncture.[12,13]

PHARMACOLOGIC THERAPY

Topical Medications

A meta-analysis of seven randomized, controlled trials[12] showed a benefit of treatment with topical nonsteroidal antiinflammatory drugs (NSAIDs) similar to that with oral NSAIDs but with fewer adverse effects. Their use should precede use of oral NSAIDs, although they are less practical when more than one joint is involved. The use of topical capsaicin is not recommended, given a paucity of high-quality data as well as small effect sizes.[12]

Oral NSAIDs

When the use of topical NSAIDs is impractical, ineffective, or not preferred, oral NSAIDs are the oral medication of choice in the absence of contraindications[12,13]; a meta-analysis of nine randomized, controlled trials (excluding trials with very-low-quality ratings) showed small effect sizes for pain and function.[12] A careful history taking and screening measurement of creatinine before the initiation of use of oral NSAIDs, use of the lowest dose for the shortest period of time, and use "as needed" can reduce the risk of adverse effects. Guidelines support the use of nonselective NSAIDs, preferably with proton-pump inhibitors, or cyclooxygenase-2 (COX-2) inhibitors in patients with no coexisting conditions.[12] A meta-analysis of eight randomized, controlled trials showed 50 fewer gastrointestinal adverse events per 1000 persons receiving COX-2 inhibitors than in those receiving nonselective NSAIDs for knee osteoarthritis.[12]

In patients with cardiovascular coexisting conditions, the use of oral NSAIDs is not recommended.[12,13] A meta-analysis that used data from

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nearly 500,000 individual patients showed that any NSAID use was associated with an increased risk of myocardial infarction[36]; associated risks may vary among COX-2 inhibitors[36,37] and nonselective NSAIDs.[38]

Other Medications

Systematic reviews and meta-analyses of randomized trials of acetaminophen in persons with knee osteoarthritis suggest minimal efficacy.[39-41] Short-term or episodic use of acetaminophen may be considered in persons who cannot use NSAIDs.[13] Regular use of acetaminophen warrants monitoring for hepatotoxic effects. In meta-analyses, the use of glucosamine or chondroitin sulfate or products containing a combination of these compounds did not lead to greater reductions in joint pain than placebo.[42,43]

Duloxetine, a serotonin and norepinephrine reuptake inhibitor that has antidepressant, central pain inhibitory, and anxiolytic activities, was efficacious in unselected patients with knee osteoarthritis.[44,45] Duloxetine may be particularly useful in patients who have widespread pain or depression.[12,46]

Tramadol, a mu opioid–receptor agonist and weak serotonin and norepinephrine reuptake inhibitor, may be considered in very limited contexts in which NSAIDs are contraindicated or ineffective and the pain is severe. Its use must be weighed against addiction potential and a possible association with increased mortality.[47] There is no role for other opioids in the management of osteoarthritis.

Intraarticular Therapies

Intraarticular glucocorticoid injections are efficacious for short-term pain relief, commonly lasting a few weeks, and may be a useful adjunct therapy, particularly for an upcoming life event. A recent randomized trial showed that physical therapy was similarly effective in the short term and better in the long term than a glucocorticoid injection.[48] Regular injections are not recommended; in patients with symptomatic knee osteoarthritis, 2 years of treatment with triamcinolone, administered intraarticularly every 3 months, resulted in greater loss of cartilage volume than saline injections.[49] There is insufficient evidence to support a meaningful effect of intraarticular hyaluronic acid; a meta-analysis showed modest effect sizes and a risk of serious adverse events (e.g., injection-site reaction and joint swelling).[50]

SURGERY

Arthroscopic partial meniscectomy has been frequently performed in patients who have knee osteoarthritis with meniscal damage. However, a meta-analysis of nine randomized trials comparing this procedure with nonsurgical treatments, including physical therapy, showed small benefits of uncertain clinical significance in the 6 months after surgery that dissipate by 1 to 2 years as well as no significant improvement in knee function.[51] A clinical practice guideline[52] and systematic review[53] strongly recommended against arthroscopic partial meniscectomy in nearly all patients with knee osteoarthritis (with the possible exception of those who had objective knee locking).

In persons with advanced osteoarthritis whose pain is not controlled with other interventions, knee replacement should be considered. Knee replacement has been associated with marked abatement of pain, improvement in function, and high rates of patient satisfaction.[54]

AREAS OF UNCERTAINTY

It is uncertain what medication to use if NSAIDs cannot be used in the treatment of knee osteoarthritis; current options are limited. No drugs are currently approved as osteoarthritis disease–modifying agents. Preliminary data from randomized, phase 2 trials have suggested improvements in joint cartilage thickness with the use of a recombinant human fibroblast growth factor 18[55] or a cathepsin K inhibitor[56] over a period of 2 years, but the clinical significance of the changes is unclear, and more data are needed. Studies are needed to assess the effects of intensive physical activity on structural outcomes. There is uncertainty regarding specific criteria on which to base referral for knee replacement.

GUIDELINES

Recently published guidelines from the American College of Rheumatology and the Osteoarthritis Research Society International (OARSI)[12,13] base recommendations predominantly on ran-

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domized, controlled trials but also acknowledge limitations of the available data, including potential publication bias, limited generalizability of findings, inadequate blinding for certain interventions, and the short duration of trials relative to a decades-long disease. OARSI guidelines provide separate recommendations for persons according to the presence and type of coexisting conditions (gastrointestinal conditions, cardiovascular disease, frailty, and widespread pain or depression)[12]; the recommendations were based on meta-analyses and quality assessments of trials but, in the absence of high-quality data for many treatments, relied on indirect evidence combined with expert opinion. The recommendations in this article are generally concordant with both sets of guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The presentation of the patient described in the vignette is characteristic of knee osteoarthritis. I would confirm this by physical examination, obtain radiographs of the knees to determine disease severity, and conduct a careful history taking with respect to other medical conditions, physical activity level, diet, patterns of weight change, functional limitations, depressive symptoms, sleep impairment, and more widespread pain. I would refer the patient for physical therapy to further assess functional status and to initiate a personalized exercise program. I would treat the patient with a topical NSAID as needed. If this is impractical or ineffective, I would recommend treatment, as needed, with either an oral NSAID plus a proton-pump inhibitor or a COX-2 inhibitor. Ongoing follow-up is needed to monitor adverse effects of medication, symptoms, weight, changes on joint examination, functional decline, physical activity, adherence to an exercise program, and barriers to treatment. I would encourage the patient to continue hiking.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

REFERENCES

1. Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. J Rheumatol 2006;33:2271-9.
2. Nguyen US, Zhang Y, Zhu Y, Niu J, Zhang B, Felson DT. Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. Ann Intern Med 2011;155:725-32.
3. Gill TM. Do the tenets of late-life disability apply to middle age? Ann Intern Med 2017;167:818-9.
4. Sharma L, Hochberg M, Nevitt M, et al. Knee tissue lesions and prediction of incident knee osteoarthritis over 7 years in a cohort of persons at higher risk. Osteoarthritis Cartilage 2017;25:1068-75.
5. Roemer FW, Kwoh CK, Hannon MJ, et al. What comes first? Multitissue involvement leading to radiographic osteoarthritis: magnetic resonance imaging-based trajectory analysis over four years in the Osteoarthritis Initiative. Arthritis Rheumatol 2015;67:2085-96.
6. Felson DT, Niu J, Clancy M, Sack B, Aliabadi P, Zhang Y. Effect of recreational physical activities on the development of knee osteoarthritis in older adults of different weights: the Framingham Study. Arthritis Rheum 2007;57:6-12.
7. Barbour KE, Hootman JM, Helmick CG, et al. Meeting physical activity guidelines and the risk of incident knee osteoarthritis: a population-based prospective cohort study. Arthritis Care Res (Hoboken) 2014;66:139-46.
8. Hawker GA, Stewart L, French MR, et al. Understanding the pain experience in hip and knee osteoarthritis — an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008;16:415-22.
9. 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;22:622-30.
10. Carlesso LC, Segal NA, Frey-Law L, et al. Pain susceptibility phenotypes in those free of knee pain with or at risk of knee osteoarthritis: the Multicenter Osteoarthritis Study. Arthritis Rheumatol 2019;71:542-9.
11. Sharma L, Kwoh K, Lee JJ, et al. Development and validation of risk stratification trees for incident slow gait speed in persons at high risk for knee osteoarthritis. Ann Rheum Dis 2019;78:1412-9.
12. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019;27:1578-89.
13. 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 Rheumatol 2020;72:220-33.
14. 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.
15. Juhl C, Christensen R, Roos EM, Zhang W, Lund H. Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. Arthritis Rheumatol 2014;66:622-36.
16. Quicke JG, Foster NE, Thomas MJ, Holden MA. Is long-term physical activity safe for older adults with knee pain? A systematic review. Osteoarthritis Cartilage 2015;23:1445-56.
17. Wang C, Schmid CH, Iversen MD, et al. Comparative effectiveness of Tai Chi versus physical therapy for knee osteoarthritis: a randomized trial. Ann Intern Med 2016;165:77-86.
18. Rini C, Porter LS, Somers TJ, et al. Automated Internet-based pain coping skills training to manage osteoarthritis pain: a randomized controlled trial. Pain 2015;156:837-48.
19. Bennell KL, Nelligan R, Dobson F, et al. Effectiveness of an Internet-delivered

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exercise and pain-coping skills training intervention for persons with chronic knee pain: a randomized trial. Ann Intern Med 2017;166:453-62.
20. Lawford BJ, Hinman RS, Kasza J, et al. Moderators of effects of Internet-delivered exercise and pain coping skills training for people with knee osteoarthritis: exploratory analysis of the IMPACT randomized controlled trial. J Med Internet Res 2018;20(5):e10021.
21. Rausch Osthoff A-K, Niedermann K, Braun J, et al. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. Ann Rheum Dis 2018;77:1251-60.
22. Dunlop DD, Song J, Semanik PA, et al. Objective physical activity measurement in the Osteoarthritis Initiative: are guidelines being met? Arthritis Rheum 2011; 63:3372-82.
23. Dunlop DD, Song J, Semanik PA, et al. Relation of physical activity time to incident disability in community dwelling adults with or at risk of knee arthritis: prospective cohort study. BMJ 2014;348: g2472.
24. Dunlop DD, Song J, Hootman JM, et al. One hour a week: moving to prevent disability in adults with lower extremity joint symptoms. Am J Prev Med 2019;56:664-72.
25. 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 randomized clinical trial. JAMA 2013;310:1263-73.
26. Messier SP, Resnik AE, Beavers DP, et al. Intentional weight loss in overweight and obese patients with knee osteoarthritis: is more better? Arthritis Care Res (Hoboken) 2018;70:1569-75.
27. Hall M, Castelein B, Wittoek R, Calders P, Van Ginckel A. Diet-induced weight loss alone or combined with exercise in overweight or obese people with knee osteoarthritis: a systematic review and meta-analysis. Semin Arthritis Rheum 2019;48:765-77.
28. Gersing AS, Solka M, Joseph GB, et al. Progression of cartilage degeneration and clinical symptoms in obese and overweight individuals is dependent on the amount of weight loss: 48-month data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2016;24:1126-34.
29. Brand E, Nyland J, Henzman C, McGinnis M. Arthritis Self-Efficacy Scale scores in knee osteoarthritis: a systematic review and meta-analysis comparing arthritis self-management education with or without exercise. J Orthop Sports Phys Ther 2013;43:895-910.
30. Ghazi C, Nyland J, Whaley R, Rogers T, Wera J, Henzman C. Social cognitive or learning theory use to improve self-efficacy in musculoskeletal rehabilitation: a systematic review and meta-analysis. Physiother Theory Pract 2018;34:495-504.
31. Holla JFM, van der Leeden M, Knol DL, et al. Predictors and outcome of pain-related avoidance of activities in persons with early symptomatic knee osteoarthritis: a five-year followup study. Arthritis Care Res (Hoboken) 2015;67:48-57.
32. Edwards RR, Cahalan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. Nat Rev Rheumatol 2011; 7:216-24.
33. Dixon KE, Keefe FJ, Scipio CD, Perri LM, Abernethy AP. Psychological interventions for arthritis pain management in adults: a meta-analysis. Health Psychol 2007;26:241-50.
34. Keefe FJ, Caldwell DS, Baucom D, et al. Spouse-assisted coping skills training in the management of osteoarthritic knee pain. Arthritis Care Res 1996;9:279-91.
35. Broderick JE, Keefe FJ, Bruckenthal P, et al. Nurse practitioners can effectively deliver pain coping skills training to osteoarthritis patients with chronic pain: a randomized, controlled trial. Pain 2014; 155:1743-54.
36. Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data. BMJ 2017;357:j1909.
37. Gunter BR, Butler KA, Wallace RL, Smith SM, Harirforoosh S. Non-steroidal anti-inflammatory drug-induced cardiovascular adverse events: a meta-analysis. J Clin Pharm Ther 2017;42:27-38.
38. Barcella CA, Lamberts M, McGettigan P, et al. Differences in cardiovascular safety with non-steroidal anti-inflammatory drug therapy — a nationwide study in patients with osteoarthritis. Basic Clin Pharmacol Toxicol 2019;124:629-41.
39. 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. Ann Intern Med 2015;162:46-54.
40. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet 2017; 390(10090):e21-e33.
41. Leopoldino AO, Machado GC, Ferreira PH, et al. Paracetamol versus placebo for knee and hip osteoarthritis. Cochrane Database Syst Rev 2019;2:CD013273.
42. Wandel S, Jüni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ 2010; 341:c4675.
43. Runhaar J, Rozendaal RM, van Middelkoop M, et al. Subgroup analyses of the effectiveness of oral glucosamine for knee and hip osteoarthritis: a systematic review and individual patient data meta-analysis from the OA trial bank. Ann Rheum Dis 2017;76:1862-9.
44. Chappell AS, Desaiah D, Liu-Seifert H, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. Pain Pract 2011;11:33-41.
45. Uchio Y, Enomoto H, Alev L, et al. A randomized, double-blind, placebo-controlled phase III trial of duloxetine in Japanese patients with knee pain due to osteoarthritis. J Pain Res 2018;11:809-21.
46. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet 2019;393:1745-59.
47. Zeng C, Dubreuil M, LaRochelle MR, et al. Association of tramadol with all-cause mortality among patients with osteoarthritis. JAMA 2019;321:969-82.
48. Deyle GD, Allen CS, Allison SC, et al. Physical therapy versus glucocorticoid injection for osteoarthritis of the knee. N Engl J Med 2020;382:1420-9.
49. 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;317:1967-75.
50. Rutjes AWS, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med 2012;157:180-91.
51. Thorlund JB, Juhl CB, Roos EM, Lohmander LS. Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. BMJ 2015;350:h2747.
52. Siemieniuk RAC, Harris IA, Agoritsas T, et al. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. BMJ 2017;357: j1982.
53. Brignardello-Petersen R, Guyatt GH, Buchbinder R, et al. Knee arthroscopy versus conservative management in patients with degenerative knee disease: a systematic review. BMJ Open 2017;7(5):e016114.
54. Shan L, Shan B, Suzuki A, Nouh F, Saxena A. Intermediate and long-term quality of life after total knee replacement: a systematic review and meta-analysis. J Bone Joint Surg Am 2015;97:156-68.
55. 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;322:1360-70.
56. Conaghan PG, Bowes MA, Kingsbury SR, et al. Disease-modifying effects of a novel cathepsin K inhibitor in osteoarthritis: a randomized controlled trial. Ann Intern Med 2020;172:86-95.

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