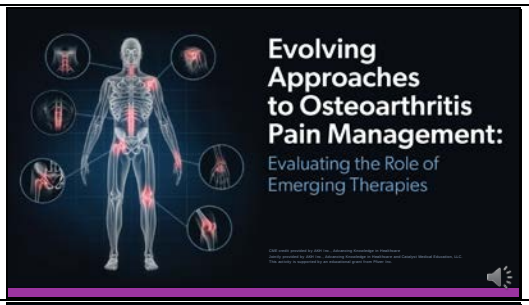
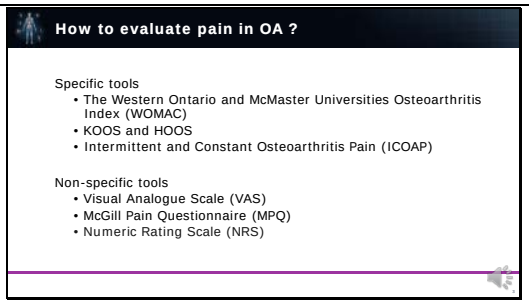
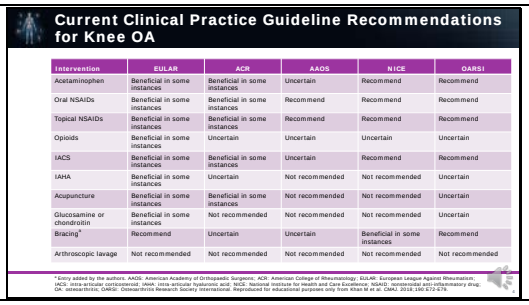
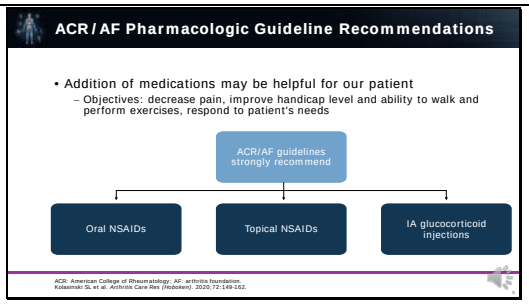
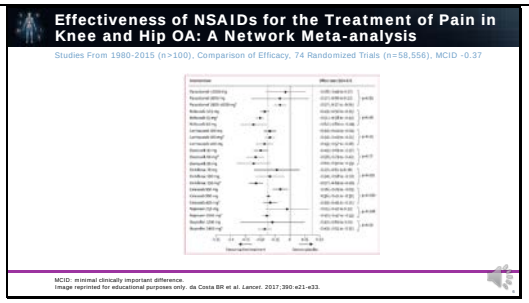
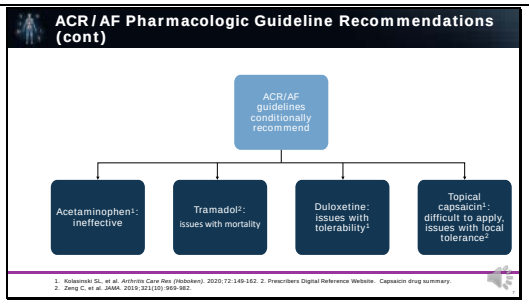
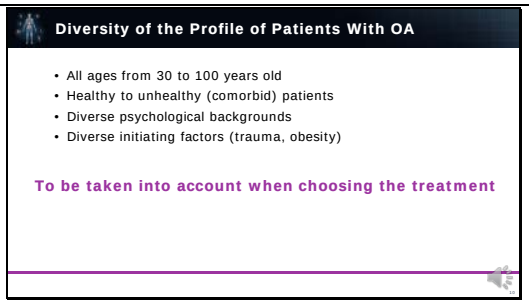
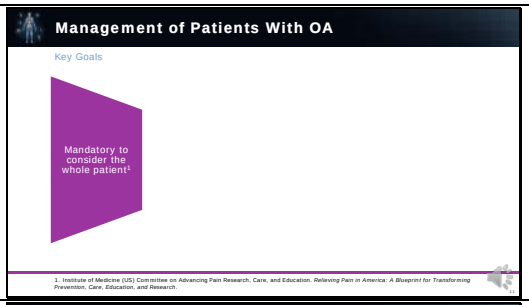
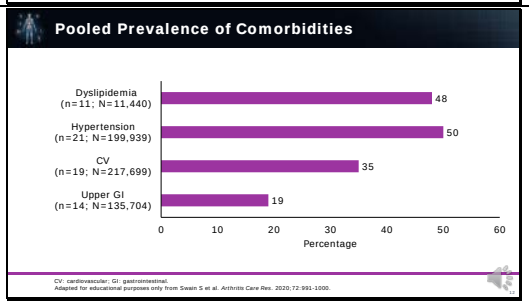
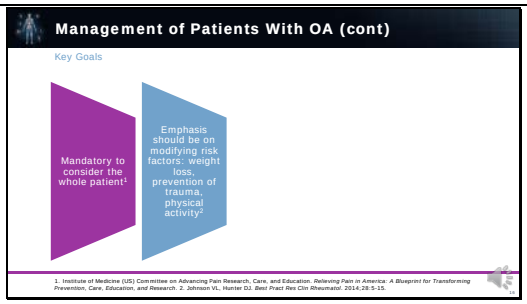
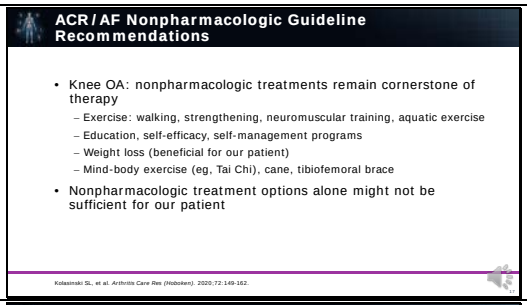
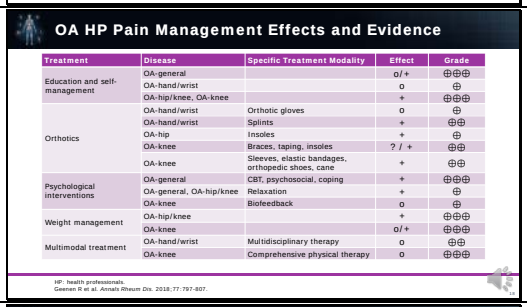
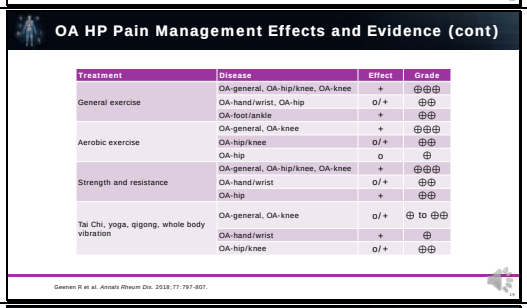
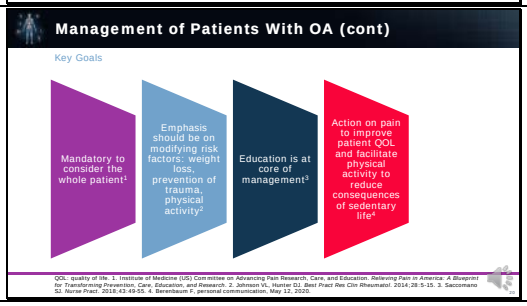
1		
2		My name is Francis Berenbaum. I am a professor of rheumatology at Sorbonne University, Saint Antoine Hospital. And we will be speaking on the evolving approaches to individualizing osteoarthritis pain management. Osteoarthritis is one of the world's leading causes of disability. This is due to its very high prevalence and the fact that this etiology causes pain and loss of joint function. Since we currently have no treatment capable of delaying the OA process, the only way to address this problem is to try to reduce the symptoms. The aim of this lecture is to show you the treatment we have available today for this, and the need to adapt this treatment to each person, to make the treatment as personalized as possible.
3		In order to optimize this treatment, it is essential to assess the patient's level of pain beforehand. For this, we have a few instruments at our disposal which are not perfect, but which allow us to get an idea of the intensity of the pain at rest or during activity. Some tools, such as WOMAC, the KOOS and HOOS, the ICOAP have been developed specifically to evaluate osteoarthritis pain, while others are more generic. It is this assessment of pain intensity that will allow the choice of treatments, and then the monitoring of the effectiveness of the treatment.
4		In order to help the clinician in their choice of treatments, we have recommendations from national and international scientific societies, the most recent having been issued by the American College of Rheumatology and the Osteoarthritis Research Society International, ORSI. In this comparative table, we note that there is a consensus only for the use of NSAIDs, as a topical

		or systemic. For the others, there is no agreement. Acetaminophen, which was initially indicated as first line in this indication, is the subject of questioning as to its real effectiveness due to a particularly modest effect size.
5		If we take the most recent published recommendations, those of the American College of Rheumatology and Arthritis Foundation, it is clear that drug treatments are a valuable aid in the management of osteoarthritis. By reducing pain, they will facilitate movement, thus reducing disability, and making walking easier. But they will also have the patient to practice exercises, which are essential for good patient care, as we shall see later. We find NSAIDs, as we have just said, but also intra-articular injections of corticosteroid, which have the advantage of being very effective, especially when there is a joint effusion. But we have the disadvantage of having an effectiveness limited in time to a few weeks.
6		This consensus to recommend NSAIDs in osteoarthritis is related to the good efficacy as shown in this Network Meta-analysis. Using 74 randomized trials involving the total of 58,556 patients, and a minimum of 100 patients for each trial, the authors analyzed the efficacy of the most commonly prescribed NSAIDs in a dose dependent-manner. The results are shown here on an effect-size basis, an indicator of the clinical relevance of the absolute difference from placebo. The dashed line represents the limit of clinical relevance. You can see that many NSAIDs, if given at the sufficient dose, go beyond this limit, although this is not spectacular. On the other hand, the lack of clinically relevant efficacy of paracetamol.

7		Other pharmacological treatments sometimes prescribed in this indication have an unfavorable risk-benefit balance. For example, studies have recently reported an association of prolonged tramadol therapy in a way with increased mortality. The causal relationship has not yet been established. But cautions should be exercised. Duloxetine is not always well tolerated, with nausea, headache. And many countries do not recognize OA as an indication, limiting its prescription. Finally, topical capsaicin poses issues of local tolerance, which leads to problems of compliance by the patient.
8		As for opioids, whether weak or strong, they pose addiction problems, especially when prescribed for a chronic disease, such as OA. In addition, they have undesirable effects that can have serious consequences, especially in the elderly, a population particularly targeted in osteoarthritis, with risks for falls and confusion. Finally, among the injectable drugs, I have already talked to you about the advantages and disadvantages of corticosteroid injection. And there is also risk of supplementation, which consists of injecting hyaluronic acid, a viscous product. Numerous clinical studies have been published on this topic. And even today, there is no consensus in the medical community, because the clinical relevance of the differences observed with respect to the injection of physiological serum has not been fully demonstrated.
9		So all these generalities about treatment recommendations have to be put in the context of the individual patient's profile, as we are dealing with patients who can be very different from each other.

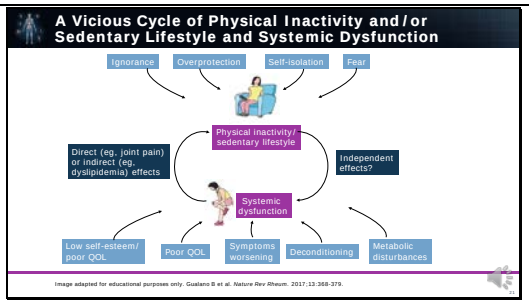
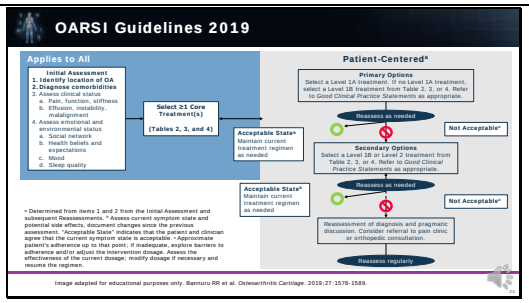
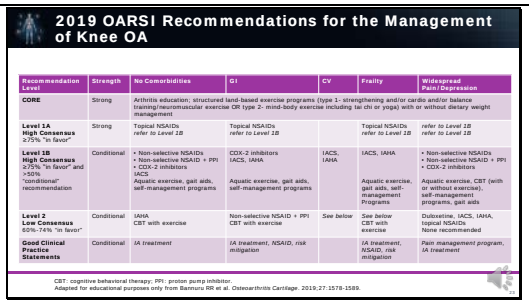
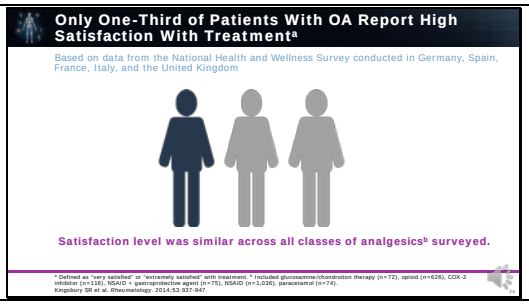
10		Osteoarthritis can affect both 30 year olds, who will develop osteoarthritis of the knee, after a skiing accident at the age of 20, and centenarians who will, inevitably, have several sites of osteoarthritis, even though it may have fewer symptoms. The OA patient may be, sometimes, a sportsman or woman, and develop post-trauma OA. But may sometimes have many comorbidities, particularly those associated with an increased cardiovascular risk, namely the elements of the metabolic syndrome, obesity, overweight, hypertension, diabetes, dyslipidemia. Finally, the psychological field plays a major role in the perception of pain in general. And therefore, of OA, in particular. The lack of management of this psychological aspect is often the main reason for the failure of medical treatment. All these elements must be considered in order to choose the appropriate treatment.
11		Thus, the first key objective in managing the symptoms of osteoarthritis is to consider the patient as a whole, and not focus solely on the intensity of pain in the affected joint.
12		Here is a systematic analysis of the type and number of comorbidities present in OA patients, based on 42 published observational studies. It shows that nearly 50 percent of patients have dyslipidemia, 50 percent have hypertension, one-third have a cardiovascular history, and one in five patients has a previous gastric problem. These figures are much higher than those observed in a non-OA population. It is quite obvious that these comorbidities will influence the symptomatic treatment to be chosen.

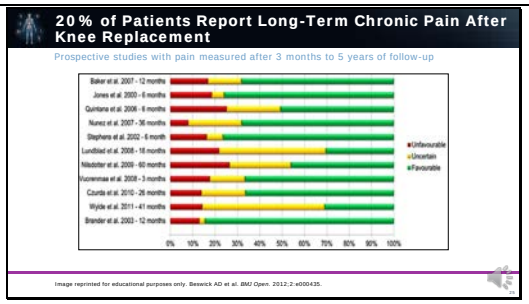
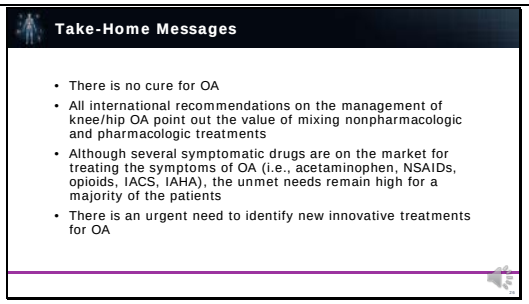
13	**Risk of NSAID-Induced Myocardial Infarction According to Co-existence of Hypertension** Hypertension Diagnosis With (N=3,672) / Without (N=4,682) aOR* / 95% CI / aOR* / 95% CI Non-selective NSAIDs Oral overall: 1.56 (1.36-1.79) / 1.32 (1.15-1.51) Parenteral overall: 3.43 (2.30-5.13) / 3.18 (2.08-4.87) • Taiwan's National Health Insurance claim database • Identification of new AMI in 2 periods: 1-30 days (case) and 91-120 days (control) • Comparison of use of NSAIDs * Conditional logistic regression adjusted for important potential time-varying confounding variables of all discordant use of antihypertensive agents, angiotensin converting enzyme inhibitors or aldosterone receptor blockers, calcium channel blockers, statins, insulin, sulfonylurea, thiazolidinedione, and aspirin between case and control period. AMI: acute myocardial infarction; aOR: adjusted odds ratio. Shau WY et al. *BMC Cardiovascular Disorders*. 2012;12:4.	For example, the risk of myocardial infarction on NSAIDs is greater when there is underlying hypertension than when there is none, as this study shows. The authors conducted a case crossover study using the Taiwan's National Health Insurance Claim Database. They identified patients with new myocardial infarction hospitalized in 2006. They defined one to 30 days prior to the admission as case, and 91 to 120 days prior to the admission as matched control period for each patient. There is an increase in the relative risk of infarction from 1.32 when the patient doesn't have hypertension, to 1.56 when the patient is hypertensive.
14		So this problem of cardiovascular safety of NSAIDs has been widely and extensively studied in the recent years, as this slide shows. You can see here the mechanisms underlying adverse cardiovascular events associated with NSAIDs. It shows cyclooxygenase-1, or COX-1, and cyclooxygenase-2, or COX-2, products in the vasculature, heart, and kidneys, the processes affected, the related beneficial and adverse physiologic effects, along with the influence on the cardiovascular system, that can arise owing to NSAID use. NSAIDs can be involved in atherogenesis, thrombosis, rhythm abnormalities, hypertension, all these can lead to these cardiovascular events.
15	**Factors That Affect Prescribing Methods in Elderly Patients** General Factors **(1) "One-size-fits-all" approach not applicable** (a) All geriatric patients ≠ **(2) Physiology** (a) Renal decline (b) Hepatic decline (c) Body muscle/fat composition change **(3) Perception of pain varies** **(4) Cognitive impairment** (a) Medication literacy decline (b) Confusion about what, when, and how much medication to take **(5) Comorbidities** (a) Interactions with medications (b) Require multiple medications **(6) Polypharmacy** (a) Confusion about what, when, and how much medication to take (b) Overdosing (c) Drug-drug interactions **(7) Age-related factor interactions with medication** (a) Increased susceptibility (b) Atypical presentation (c) Delayed/lack of detection **(8) Evidence-based practices** (a) Lack of a roadmap to optimally manage pain **(9) Multiplicity of providers and lack of team approach to managing health conditions in elderly patients** (a) Multiple physicians prescribing (b) Pharmacists (c) Self/consumer (d) Insurance companies **(10) Cost/coverage of medications** Taylor R Jr et al. *Curr Gerontol Geriatr Res*. 2012;2012:196159.	The other population often affected by OA is the elderly. This is a particularly challenging population to treat for many reasons. Physiologically, many organs no longer function normally, such as their kidney or their liver. Elderly people often take many other medications for different pathologies, which can lead to possible drug interactions, but also some of which can be dangerous, due to errors in taking them, especially the risk of cognitive impairment, a problem that increases with age.

16		Thus, it is essential to consider the treatment of a patient with OA, not only on the pharmacological, but also on the non-pharmacological side. Action on the risk factors for aggravation of OA must be the basis of the treatment. Losing weight in case of overweight, starting physical activity to help weight loss, and correction of a possible metabolic syndrome, preventing joint trauma, all these preventive measures must be addressed at the first consultation.
17		Among the exercises to be encouraged are walking, muscle strengthening, proprioceptive exercises, aquatic exercises, as well as mind-body exercises. Education and self-management programs have demonstrated their usefulness in this pathology. Finally, in some patients who feel instability in their knee, the tibia femoral brace can help the patient's stability.
18		Here are the different levels of evidence for the effectiveness of these non-pharmacological measures according to the methodology of evidence-based joint medicine. You will find education and self-management, different orthotics, weight loss, and relaxation, for example.
19		With respect to exercise, it is clear that exercise in general, aerobic exercise, and strength training are clearly effective in managing symptoms.
20		Thus, by combining pharmacological and non-pharmacological measures, one should be able to reduce the level of pain with the aim of facilitating the practice of physical exercise. These will, themselves, have a beneficial effect on OA, but will also help to combat the sedentary lifestyle that is at the root of many other chronic diseases that reduce quality of life and life expectancy.

Treatment	Disease	Specific Treatment Modality	Effect	Grade
Education and self-management	OA-general		o/+	⊕⊕⊕
	OA-hand/wrist		o	⊕
	OA-hip/knee, OA-knee		+	⊕⊕⊕
Orthotics	OA-hand/wrist	Orthotic gloves	o	⊕
	OA-hand/wrist	Splints	+	⊕⊕
	OA-hip	Insoles	+	⊕
	OA-knee	Braces, taping, insoles	? / +	⊕⊕
	OA-knee	Sleeves, elastic bandages, orthopedic shoes, cane	+	⊕⊕
Psychological interventions	OA-general	CBT, psychosocial, coping	+	⊕⊕⊕
	OA-general, OA-hip/knee	Relaxation	+	⊕
	OA-knee	Biofeedback	o	⊕
Weight management	OA-hip/knee		+	⊕⊕⊕
	OA-knee		o/+	⊕⊕⊕
Multimodal treatment	OA-hand/wrist	Multidisciplinary therapy	o	⊕⊕
	OA-knee	Comprehensive physical therapy	o	⊕⊕⊕

Treatment	Disease	Effect	Grade
General exercise	OA-general, OA-hip/knee, OA-knee	+	⊕⊕⊕
	OA-hand/wrist, OA-hip	o/+	⊕⊕
	OA-foot/ankle	+	⊕⊕
Aerobic exercise	OA-general, OA-knee	+	⊕⊕⊕
	OA-hip/knee	o/+	⊕⊕
	OA-hip	o	⊕
Strength and resistance	OA-general, OA-hip/knee, OA-knee	+	⊕⊕⊕
	OA-hand/wrist	o/+	⊕⊕
	OA-hip	+	⊕⊕
Tai Chi, yoga, qigong, whole body vibration	OA-general, OA-knee	o/+	⊕ to ⊕⊕
	OA-hand/wrist	+	⊕
	OA-hip/knee	o/+	⊕⊕

21		Physical inactivity and sedentary behavior lead to systemic dysfunction and the aggravation of symptoms. These symptoms predispose the patient to a more sedentary lifestyle. This has many negative consequences, in term of quality of life, due to an increased risk of depression, deconditioning with effort, metabolic disturbances. Altogether, there is a vicious cycle of OA, leading to physical inactivity, and sedentary lifestyle, increasing OA symptoms.
22		In conclusion, it is, therefore, essential that recommendations for the management of OA take into account this aspect of personalized treatment, as each patient is different. They must take particular account of the patient's own history and comorbidities. The most recent OARSI recommendations have tried to take this into account. Without going into the details of this busy slide, you can see on the right the algorithm to be followed, according to the response to treatment at each stage. This algorithm is initially based on an initial assessment to identify the location of OA, the comorbidities, the intensity of the different symptoms, and emotional and environmental status. Therapeutic choices are made based on different levels, called Level 1A, 1B, or 2.
23		You see here the definitions of these levels, which are adapted according to the presence of different comorbidities, such as gastrointestinal comorbidities, cardiovascular comorbidities, the existence of a frailty or depressive background, or subject to widespread pain. These recommendations are of course more complicated to synthesize than other simple ones. But they have the advantage of being closer to a personalized medicine, therefore more useful for the doctor in his or her daily practice.
24		I would like to conclude by saying that, despite everything, neither doctors nor patients are satisfied with the treatments used in osteoarthritis, as shown here by this survey, carried out in several European countries. In the end, only one-third of patients are really satisfied, which is very low.

25		Unfortunately, total knee replacement is not a panacea. You have here an analysis of several prospective studies in patients who have undergone total knee prosthesis surgery. It shows that the proportion of people with an unfavorable long-term pain outcome, ranged from about 10 percent to 34 percent after knee replacement. In the best quality studies, an unfavorable pain outcome was reported in about 20 percent of patients after knee replacement. And we do not know yet the determinants of good and bad outcome.
26		So here are my take-home messages. There is no cure for osteoarthritis. All international recommendations on the management of knee or hip OA, point out the value of mixing non-pharmacologic and pharmacologic treatments. Although there are several symptomatic drugs are on the market for treating the symptoms of OA, like acetaminophen, NSAIDs, opioid, intraarticular corticosteroid, or intraarticular hyaluronic acid, the unmet needs remain high for majority of the patients. So there is an urgent need to identify new innovative treatments for OA. Thank you for your attention.