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Recommendations of the French Society of Rheumatology on pharmacological treatment of knee osteoarthritis

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Abstract

Objectives

To establish recommendations for pharmacological treatment of knee osteoarthritis specific to France.

Methods

On behalf of the French Society of Rheumatology (SFR), a bibliography group analyzed the literature on the efficacy and safety of each pharmacological treatment for knee osteoarthritis. This group joined a multidisciplinary working group to draw up recommendations. Strength of recommendation and quality of evidence level were assigned to each recommendation. A review committee gave its level of agreement.

Results

Five general principles were established: 1) need to combine pharmacological and non-pharmacological treatments, 2) personalization of treatment, 3) symptomatic and/or functional aim of pharmacological treatments, 4) need to regularly re-assess the treatments and 5) discussion about arthroplasty if medical treatment fails.

Six recommendations involved oral treatments: 1) paracetamol should not necessarily be prescribed systematically and/or continuously, 2) NSAIDs, possibly as first-line, 3) weak opioids, 4) strong opioids, 5) symptomatic slow-acting drugs of osteoarthritis, and 6) duloxetine (off-label use). Two recommendations involved topical agents (NSAIDs and capsaicin <1%). Three recommendations involved intra-articular treatments: corticosteroid or hyaluronic acid injections that can be proposed to patients. The experts did not draw a conclusion about the benefits of platelet-rich plasma injections.

Conclusion

These are the first recommendations of the SFR on the pharmacological treatment of knee osteoarthritis.

Keywords: knee osteoarthritis, osteoarthritis, treatment, recommendations

Introduction

In France, symptomatic knee osteoarthritis (OA) affects 2.1% to 10.1% of women and 1.6% to 14.9% of men between 40 and 75 years of age [1]. The risk factors for knee OA are well known: obesity and metabolic diseases, aging and joint trauma [2]. This location represents 85% of the burden caused by OA in general [3].

Pain—the main symptom of knee OA—is not well correlated with radiographic findings, implying that complex mechanisms are at play [4]. When associated with stiffness and functional discomfort, it impacts the patients' quality of life. In addition, the physical disability related to knee OA is associated with high cardiovascular mortality given the patients' sedentary nature [5]. In France, medical treatment of knee OA is multidisciplinary, involving rheumatology, general medicine, orthopedics, physical medicine and rehabilitation, pain control and geriatrics. Depending on each provider's specialty and habits, the treatment approaches can differ.

The management of knee OA combines pharmacological and non-pharmacological treatments. There are numerous pharmacological treatments, thus it is essential to master their prescription. The existing international recommendations of the Osteoarthritis Research Society International (OARSI), European League Against Rheumatism (EULAR), American College of Rheumatology (ACR) and the American Academic of Orthopaedic Surgeons (AAOS) are not well suited to France, given the between-country differences in the availability and reimbursement of medications, drug prescription habits and care pathways [6-10]. Moreover, the elimination of reimbursement of certain drugs by the French Social Security system (symptomatic slow-acting drugs of OA [SYSADOA] and intra-articular hyaluronic acid [HA] injections) requires that these treatments be correctly positioned in the treatment scheme. This prompted the OA group of the French Society of Rheumatology (SFR) to established recommendations on the use of pharmacological treatments for knee OA to standardize practices and improve patient care.

Methods

The recommendations were elaborated according to EULAR standard operating procedures [11, 12]. Six rheumatologists (AC, AL, CR, FE, PO, SF) carried out a literature review (frozen on March 1, 2018). The main working document was the OARSI recommendations published in 2014 [8]. The bibliography group also included randomized clinical trials with more than 100 enrolled patients published since the 2014 OARSI recommendations in their analysis of the literature, along with systematic reviews and meta-analyses. They evaluated the effectiveness of pharmacological treatments on pain and function, along with their structural effect and tolerance. The potential effect of HA injections on delaying arthroplasty was studied. For safety, cohort studies were also retained. Searches were done using the Medline database and with conference abstracts (ACR, EULAR, OARSI) over the past 3 years.

The bibliography group then merged with the working group, which consisted of 21 physicians (hospital-based rheumatologists and/or in private practice, one rehabilitation physician, one orthopedic surgeon, two chronic pain specialists, one general practitioner) and one patient. All the participants in the working group provided a conflict of interest statement to the SFR's ethics committee prior to participating.

Every general principle and every recommendation were adopted if a consensus was achieved ($\geq 80\%$ of voters). If the vote was $< 80\%$, the recommendation was discussed again. Several voting rounds were allowed. Before the 1st vote, each member of the working group provided his/her level of agreement (numerical scale from 0 to 10, where 0 is complete disagreement and 10 is complete agreement) with each principle and recommendation.

A multidisciplinary review committee (composed of 31 members) then provided their level of agreement. For each treatment modality, the quality of evidence and strength of recommendation were defined [11].

These recommendations apply to symptomatic tibiofemoral knee OA in adults and its pharmacological treatments, i.e. molecules that have been approved as drugs, medical devices (HA injection) and injections of platelet-rich plasma (PRP). Dietary supplements

were excluded. These recommendations are aimed at physicians (rheumatologists, general practitioners, orthopedic surgeons, physical medicine and rehabilitation doctors and chronic pain specialists), paramedical professions, patient associations and health authorities.

Results

The output consisted of 5 general principles and 11 recommendations (**Table 1**). The review committee's level of agreement is shown in **Table 2**.

1. GENERAL PRINCIPLES

1.1 Optimal treatment of knee OA must include non-pharmacological measures

These pharmacological recommendations are not dissociable from non-pharmacological treatments, which will be described later.

1.2 Pharmacological treatment of knee OA must be personalized

The following features must be considered when prescribing a medication: 1) age, patient comorbidities and on-going treatments, 2) intensity of symptoms and their impact, 3) efficacy and safety of previously prescribed treatments.

1.3 Pharmacological treatments are given solely to address symptoms and function

There is insufficient evidence in the literature for a potential chondroprotective effect of any of the treatments evaluated, i.e. slowing down cartilage loss. Studies have shown a significant structural effect of certain molecules, without this being considered relevant at the individual scale [13]. Thus, pharmacological treatments for knee OA are prescribed based on the patient's symptoms and the findings of the clinical examination.

1.4 Given the age and comorbidities of the knee OA population, any pharmacological treatment must be re-evaluated regularly

Knee OA is a chronic condition that can have different types of progression (chronic background pain, with or without acute flare-ups) requiring regular assessments to guide the drug prescriptions [14–17]. An ineffective and/or poorly tolerated treatment must be stopped, and one must make sure there are no contraindications or drug interactions (e.g., anticoagulants/oral non-steroidal anti-inflammatory drugs [NSAIDs]). It is also necessary to check how often each prescribed drug is taken, which may reflect on pain intensity, and not renew a prescription for a treatment that has become unnecessary. The treatments must be re-evaluated by a physician. The patient's ability to comply with the prescription must also be taken into consideration.

1.5 Knee arthroplasty must be discussed with the patient who has symptomatic knee OA, with confirmed structure damage, causing disability that hinders quality of life, despite well conducted pharmacological and non-pharmacological treatment

These recommendations do not aim to define the type of implant, choice of material nor the surgical approach, which are the domain of the orthopedic surgeon. It is important to consider the patient's choice when deciding on joint replacement, along with the symptoms and disability brought on by their knee OA. A function and pain questionnaire such as the Lequesne index can help make the decision about the surgical indication [18]. A conservative surgery such as re-alignment osteotomy has specific indications that are outside the scope of these recommendations.

2. RECOMMENDATIONS

2.1 Paracetamol must not necessarily be prescribed systematically and/or continuously

The working group noted only a very modest effectiveness of paracetamol (minimal effect size < 0.20), which was statistically significant but not clinically relevant on an individual scale [8, 19]. More than 3 g/day of paracetamol does not provide any supplementary benefit [20]. Furthermore, several cohort studies and one randomized trial have reported potentially severe side effects when paracetamol is taken long-term: cardiovascular events, increased blood pressure, increased frequency of gastrointestinal (GI) side effects, anemia potentially tied to GI system [19–22]. Thus, the working group believes that paracetamol can be prescribed as a secondary symptomatic treatment; however, its efficacy and safety profile do not make it suitable for prescription as long-term primary therapy. The benefits of renewing it must be determined during follow-up visits.

2.2 Oral NSAIDs must be used for the shortest time and at the lowest effective dose possible. They can be proposed as first-line therapy if there are no contraindications or cardiovascular risk factors and/or risk factors for gastrointestinal complications. The prescription and choice of NSAID must take into account the patient's comorbidities and must be prescribed after providing information about adverse effects.

The working group recognized the analgesic and functional effectiveness of oral NSAIDs, as proven in several recent meta-analyses [19,20]. Thus, oral NSAIDs are positioned as a first-line therapy after verifying the absence of contraindications and the precautions for use. The working group highlighted the benefits of this class of drugs for inflammatory flare-ups (expert opinion).

Patient age, on-going treatments (especially anticoagulants and anti-aggregants), the presence of comorbidities (cardiovascular, GI, renal) and NSAID allergies must be considered when prescribing them. Given their safety profile, oral NSAIDs must be used at the minimum effective dose i.e. resulting in perceptible symptom relief, during the shortest

amount of time possible. The molecule will be selected based on the patient's comorbidities (GI and/or cardiovascular and/or renal) (expert opinion).

Either selective (COX-2 inhibitors) or non-selective oral NSAIDs can be prescribed. The literature suggests that naproxen has the most acceptable safety profile in terms of cardiovascular events, with fewer events of this type in comparison with diclofenac or celecoxib. Conversely, naproxen could be associated with more GI events than these two molecules [23]. The increased risk of CV events with diclofenac emerges from the first month of treatment [24]. Co-prescription of selective or non-selective NSAIDs with a proton pump inhibitor should be considered according to the marketing authorization application in France, based on the patient's risk factors and history.

The working group highlighted the other potential side effects of oral NSAIDs (hepatic, renal, cutaneous). The frequency of NSAID side effects increases with the dose, with no additional improvement in terms of effectiveness. The other systemic administration routes (intramuscular, intravenous) of NSAIDs have no place in treating knee OA.

2.3 Topical NSAIDs can be proposed

The analgesic effectiveness of topical NSAIDs (primarily ketoprofen or diclofenac) for musculoskeletal pain mainly due to OA has been reported in two meta-analyses [25,26]. The number needed to treat (NNT) is 9.8 (95% confidence interval (CI): 7.1-16) for diclofenac and 6.9 (95% CI: 5.4-9.3) for ketoprofen [26]. Despite potential biases, the effectiveness of topical NSAIDs appears to be comparable to that of oral NSAIDs [26]. The safety profile of these drugs is satisfactory, giving them a good risk-benefit profile in a population of knee OA patients who have comorbidities and/or are older. A reminder that the ANSM (French National Agency for Medicines and Health Products Safety) put out an alert about the risk of photosensitivity with topical ketoprofen. The working group insisted on the need for daily application of topical NSAIDs on the symptomatic compartment of the knee, and the need to check good treatment compliance (expert opinion).

2.4 Weak opioids, alone or in combination with paracetamol, may be proposed for analgesic purposes and must be prescribed while taken into account comorbidities and after providing information about adverse effects

The comments about this recommendation are grouped with those of the next recommendation.

2.5 Strong opioids must only be prescribed to patients who have a contraindication to knee surgery, who have failed or have a contraindication to other treatments, while taking into account comorbidities and after providing information about adverse effects

Weak opioids (codeine, opium extract, tramadol) and strong opioids (morphine and oxycodone) are often studied together. Based on randomized controlled studies and meta-analyses, the clinical effectiveness of strong and weak opioids is considered modest against OA pain [27,28]. The NNT is 10 for strong opioids or codeine [28]. A “treat-to-target” study in patients suffering from low back pain, hip OA or knee OA found no clinical analgesic superiority of strong opioids relative to various non-opioid drugs (but including tramadol) [29]. This modest effectiveness should be balanced with the risk of severe side effects or side effects leading to treatment discontinuation [27,28].

As for tramadol, a recent study in OA patients found a significant relationship between tramadol intake prescribed for an average of 22 days (min 5, max 67) and mortality within 1 year, although the authors could not make any conclusions about causality [30]. A Cochrane meta-analysis on tramadol in OA (dosage of 37.5 to 400 mg/day) [31], which was recently updated [32], found modest efficacy of tramadol alone or in combination with paracetamol: analgesic and functional efficacy close to threshold for clinical relevance but with significantly more patients reporting large pain and functional improvements (defined as 20% or more

improvement) than when taking placebo. However, tramadol use was associated with significantly more adverse effects.

Before prescribing any opioids, it is important to assess the risk of side effects in a given patient based on his/her age and comorbidities and to inform patients of the potential side effects, particularly the risk of falls (expert opinion). Given their safety profile, the review committee contends that using strong opioids in knee OA must be reserved for patients who have a contraindication to knee surgery, or when other treatments have failed or are contraindicated (expert opinion). In older patients, intra-articular injections are preferred (corticosteroids if not contraindicated and/or hyaluronic acid) (expert opinion).

2.6 Intra-articular corticosteroid injections can be proposed, especially for inflammatory flare-ups with joint effusion

The level of agreement for this recommendation is high and is based on publications with a high quality of evidence (meta-analysis of randomized controlled trials) [33]. In the presence of joint effusion, any intra-articular corticosteroid injection must be preceded by joint aspiration to reduce pain and to analyze the synovial fluid at least once (expert opinion). The group highlighted the benefit of intra-articular corticosteroid injection in cases of inflammatory flare-ups; however there is little literature on this topic (expert opinion) [34,35]. There is currently no consensus definition of an inflammatory flare-up.

It is not possible to make a definitive choice between the different types of injectable corticosteroids; however, triamcinolone hexacetonide injectable suspension (2%, 2 mL) is preferred, especially in cases of substantial or refractory joint effusion. With triamcinolone hexacetonide, one must confirm the intra-articular position of the needle during the injection (presence of synovial fluid or imaging guidance). The choice of which product to inject also depends on its availability. Repeating the corticosteroid injection, depending on the clinical response, should be discussed on a case-by-case basis and take into account the safety, comorbidities and number of prior injections. Safety related to systemic diffusion of intra-

articular corticosteroids relative to blood pressure control and glycemic control is essential when deciding on the injection and during monitoring.

Corticosteroid injections have been said to have a deleterious effect on structural progression of the knee OA [36,37]. In a randomized controlled trial, the extent of progression was low on an individual scale and the frequency of the injections (every 3 months for 2 years) was not orchestrated by the symptoms, which does not correspond to clinical practice in France [37]. If arthroplasty is a possibility in the short term, it is preferable to avoid corticosteroid injections.

2.7 Intra-articular hyaluronic acid injections can be proposed, without expecting a chondroprotective effect

Proof of efficacy for HA injections is derived from several meta-analyses of randomized controlled trials. It has attained a high level of agreement confirming the role of HA injections in the treatment arsenal for symptomatic knee OA [38–41]. Their effectiveness has been demonstrated versus placebo [38,42]. A meta-analysis focused solely on high-quality placebo-controlled studies showed a benefit—albeit modest—of intra-articular HA injections on pain and function at 3 months [38]. The effectiveness of intra-articular HA injections does not appear to differ from that of oral NSAIDs [19,43] although we cannot rule out the possibility of a larger placebo effect related to the intra-articular administration route [44].

Randomized trials [45,46] and two meta-analyses [47,48] have raised doubt about the effectiveness of HA injections. One of these meta-analyses included only two studies of Hylan-GF20, limiting the scope of its conclusions [48], while the study by Rutjes et al.—which questioned both the efficacy and safety—has been criticized [47, 49]. However, it is important to consider the potential iatrogenic effect of any intra-articular procedure. HA takes longer to be effective than corticosteroid injections [50–53].

Some studies, mainly done in the USA, have suggested that HA injections are likely to delay the need for knee arthroplasty, although some of these studies have methodological biases [54–56].

The working group insisted on the fact that HA injection only have effects on knee OA symptoms; the structural effect of HA injections is not sufficiently robust to suggest this treatment for chondroprotective purposes. The elimination of reimbursement of HA injections by the French Social Security system has not cast doubt on their benefits for treating symptomatic knee OA.

The experts agreed on the fact that HA injections should be proposed in cases of symptomatic knee OA with no or minimal joint effusion. The effectiveness of the HA is independent of its molecular weight. Based on the literature, we cannot conclude on the effectiveness of single versus multiple injections (3 times) for HA products having both options [57,58]. Repeating these injection cycles, based on the therapeutic response, should be discussed on a case-by-case basis.

Safety is satisfactory except for rare cases of septic arthritis or local reactions [59] particularly in comparison with oral treatments (paracetamol, NSAIDs) [19].

2.8 Symptomatic slow-acting drugs of osteoarthritis (avocado and soybean unsaponifiables, chondroitin, glucosamine, diacerein) can be proposed, without expecting a chondroprotective effect

The working group recognized that, while symptomatic slow-acting drugs of OA (SYSADOA) remain in the therapeutic arsenal for knee OA, their efficacy is weak [60–65]. These treatments can be proposed for symptomatic knee OA, without expecting an important clinical benefit. Their effects on pain and functional discomfort related to OA can be observed in a statistically significant manner relative to a placebo; however, the clinical relevance of this effect on an individual scale is controversial. A reminder that the ANSM has contraindicated diacerein in those older than 65 years and in those with history of liver

disease. Furthermore, the *Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail* (ANSES) discourages the consumption of dietary supplements containing glucosamine—with or without chondroitin sulfate—by persons who are diabetic or prediabetic. Also, these molecules do not have a relevant chondroprotective effect on an individual scale [64].

2.9 Low-dose topical capsaicin (< 1%) can be considered

This treatment was mentioned in the 2014 OARSI recommendations [8]. The effectiveness of low-dose topical capsaicin (<1%) is based on a systematic review of literature that showed an analgesic effect in knee OA patients after 4 weeks [66]. However, low-dose topical capsaicin caused local side effects (minor burns) in 35% to 100% of patients. Such symptoms bring into question how well a study's blinding can be maintained and limits the impact of its effectiveness findings. This treatment is not typically associated with notable systemic adverse effects.

The prescription of capsaicin < 1% can be obtained by a masterful preparation. In terms of topical treatments, the working group recognized that topical NSAIDs were simpler to prescribe, had longer follow-up and more knowledge associated with them.

2.10 Off-label duloxetine can be considered in the absence of therapeutic alternatives

This treatment option is mainly based on a meta-analysis of three controlled randomized trials showing consistent effectiveness of duloxetine in relieving pain symptoms (30 mg/day initially, then increased up to 60–120 mg/day) [67]. In terms of safety, side effects are statistically more frequent when taking duloxetine than placebo, with a higher risk of discontinuance. There were no more severe side effects when taking duloxetine than placebo. Given that duloxetine is not approved in this indication in France, it should only be prescribed when there are no other treatment alternatives.

2.11 No conclusions could be made on the benefits of intra-articular injections of platelet concentrates given the lack of follow-up and insufficient data

The literature is very active on this topic, with several meta-analyses and randomized trials versus HA. However, the injection protocols differ greatly in terms of preparation methods, whether white blood cells are present in the PRP, number of centrifugation rounds, number of injections, injection volume, ultrasound-guided injection, making it difficult to analyze the literature.

The safety of this type of treatment appears satisfactory at least in the short and medium term.

When preparing these recommendations, the working group considered that there was insufficient robust published data both on the effectiveness and the safety to recommend or not recommend this type of treatment. Better designed studies are needed to minimize the analysis bias. PRP injections have mainly been the subject of open-label studies or compared to HA injections. When these recommendations were drawn up, there were no randomized, placebo-controlled studies that had good methodological quality and/or included enough patients.

Discussion

This is the first set of French recommendations about pharmacological treatments for knee OA on behalf of the SFR. There was a high level of agreement in the working group about the general principles. Looking for cardiovascular, GI, renal, and hepatic comorbidities, while also considering age and the risk of drug interactions are simple but essential concepts to follow when tailoring the treatment decision to each patient. This is particularly important when prescribing oral NSAIDs, opioids or corticosteroid injections, given their known side effects. Depending on the patient, therapeutic solutions with less iatrogenic potential should be considered (e.g. topical NSAID, HA injection).

One of the principles of these recommendations is the aim of these pharmacological treatments: they should be prescribed to address symptoms, i.e. reduce pain and improve function. No available treatment has demonstrated a structural effect in a sufficiently robust manner to be relevant at an individual scale.

The recommendations on paracetamol, oral and topical NSAIDs, weak and strong opioids, and intra-articular corticosteroid or HA injections also have strength of agreement ≥ 9 out of 10. Oral NSAIDs are the cornerstone of the pharmacological arsenal for knee OA, while keeping in mind their contraindications and precautions for use. Despite its low level of efficacy, paracetamol can be considered, especially in patients who have contraindications to oral NSAIDs. However, given recent data on its GI, cardiovascular or hepatic safety [21,22], paracetamol is not positioned as a routine long-term treatment; instead it is prescribed upon request, based on the symptoms. This is a change in paradigm for its use in France.

The 2019 updated OARSI recommendations also emphasize the benefits of topical NSAIDs given their efficacy and safety profile and have highlighted the benefits of intra-articular HA injections relative to prior recommendations [10]. The recommendations about topical capsaicin, duloxetine and intra-articular PRP injections had an agreement score of 8.2. It is likely that French physicians have little experience with topical capsaicin < 1% despite well-conducted clinical trials. Topical capsaicin, given its strength of evidence for efficacy and safety, was dropped from the latest OARSI recommendations, although it is recommended conditionally by the ACR [7, 10]. While duloxetine has been studied in randomized controlled trials, it is not approved for the knee OA indication in France, limiting its prescription and thus medical experience with its use in this indication. Although duloxetine was recommended by the OARSI in 2014 in patients who have knee OA or diffuse OA without comorbidities and those who have diffuse OA with comorbidities, this treatment is recommended in the 2019 update in patients with knee OA who also have depression or fibromyalgia [8,10]. The score and standard deviation of intra-articular PRP injections can be explained by the variability in practices and interpretation of the analysis of literature, which is heterogenous and variable

in quality. An update to the recommendations will be important for this treatment modality. In 2019, the OARSI and ACR recommended against using PRP in knee OA [7, 10].

Certain treatments were the subject of a literature analysis, but not a specific recommendation. Consequently, the following are not recommended for the pharmacological treatment of knee OA symptoms: bisphosphonates, vitamin D, gabapentin, pregabalin, statins, methotrexate, calcitonin, and TNF inhibitors.

Since these recommendations were prepared, other treatments (intra-articular injections of stem cells, anti-nerve growth factor) have been studied and will likely be included in a future update. Stem cell injections are not recommended by the OARSI and ACR [7,10].

The working group contends that intra-articular corticosteroid injections can be proposed to patients with symptomatic knee OA. These treatments should be considered in patients who have contraindications to other treatments (oral NSAIDs or opioids). More recently, studies have criticized the safety profile of intra-articular corticosteroid injections, suggesting an increased risk of structural deterioration [36,37]. However, the worsening identified was modest on an individual scale and does not cast doubt on their use upon request to control symptoms of knee OA, without repeating injections if there is no efficacy.

The reimbursement for SYSADOA and intra-articular HA injections has been eliminated by the French Social Security system. However, these treatments continue to be part of the treatment arsenal for symptomatic knee OA. The effectiveness of SYSADOA is modest, which limits the expected benefit of their prescription. As for HA injections, the working group believes their efficacy level and safety profile make them an important therapeutic tool for symptomatic knee OA. The elimination of reimbursement will—to some extent—limit their access and their use. It would be interesting to see if this elimination of reimbursement, which was implemented in 2017, will result in the use of treatments that have a worse safety profile (opioids, oral NSAIDs) or lead to increased number of knee replacement procedures.

Duloxetine and topical capsaicin had a low level of agreement in the review committee for the same reasons as those outlined to explain the score assigned by the working group. PRP

injection is the only recommendation with a higher agreement score in the review committee than the working committee, indicating diverging opinions about this treatment.

The strength of these recommendations is that they were prepared by a working group who had expertise in both clinical trials on knee OA and clinical practice. This is a multidisciplinary working group, which captures all the practitioners who provide medical care for patients with knee OA. The working group also included one patient.

These recommendations provide the indications for the prescription of pharmacological treatments in knee OA. The overall care of these patients justifies the upcoming introduction of recommendations for non-pharmacological treatments.

To conclude, these are the first recommendations of the SFR on the pharmacological treatment of knee OA targeted at a large swath of healthcare professionals, and at patient associations and health authorities.

Members of review committee

Xavier Ayral, Paris; Florian Bailly, Paris Hervé Bard, Paris; Michel Bercovy, Paris; Philippe Bertin, Limoges; Valérie Briole, Paris; Alain Cantagrel, Toulouse; Van Thoai Chuong, Saint-Maurice; Thierry Conrozier, Belfort; Emmanuel Coudeyre, Clermont-Ferrand; François-Paul Ehkirch, Paris; René-Marc Flipo, Lille; Alain Francon, Aix-les-Bains; Pierre Khalifa, Paris; Sherazade Kinouani, Bordeaux; Françoise Laroche, Paris; Patrick Legoux, Puteaux; Emmanuel Maheu, Paris; Christelle N’Guyen, Paris; Gilles Pasquier, Lille; Yves-Marie Pers, Montpellier; Thao Pham, Marseille; Pedros Sanches, Franconville; Alain Sautet, Paris; Thierry Schaefferbeke, Bordeaux; Thierry Thomas, Saint-Etienne; Philippe Thoumie, Paris; Philippe Tollie, Franconville; Anne-Priscille Trouvin, Paris; Pascale Vergne-Salle, Limoges; Daniel Wendling, Besançon.

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Table 1. Recommendations on pharmacological treatment of knee osteoarthritis

	Level of agreement mean \pm SD
GENERAL PRINCIPLES	
A. Optimal treatment of knee OA must include non-pharmacological measures	9.9 \pm 0.2
B. Pharmacological treatment of knee OA must be personalized	9.9 \pm 0.2
C. Pharmacological treatments are given solely to address symptoms and function	9.3 \pm 1.3
D. Given the age and comorbidities of the knee OA population, any pharmacological treatment must be re-evaluated regularly	9.8 \pm 0.6
E. Knee arthroplasty must be discussed with the patient who has symptomatic knee OA, with confirmed structure damage, causing disability that hinders quality of life, despite well conducted pharmacological and non-pharmacological treatment	9.6 \pm 1.1
Recommendations	
1. Paracetamol must not necessarily be prescribed systematically and/or continuously (Level 1A, Strength A)	9.3 \pm 2.4
2. Oral NSAIDs must be used for the shortest time and at the lowest effective dose possible (Level 1A, Strength A). They can be proposed as first-line therapy if there are no contraindications or cardiovascular risk factors and/or risk factors for gastrointestinal complications (Level 1A, Strength A). The prescription and choice of NSAID must take into account the patient's comorbidities and must be prescribed after providing information about adverse effects (Level 4, Strength D)	9.0 \pm 2.6
3. Topical NSAIDs can be proposed (Level 1A, Strength B)	9.0 \pm 2.2
4. Weak opioids, alone or in combination with paracetamol, may be proposed for analgesic purposes (Level 1A, Strength A) and must be prescribed while taken into account comorbidities and after providing information about adverse effects (Level 4, Strength D)	9.5 \pm 0.8
5. Strong opioids must only be prescribed to patients who have a contraindication to knee surgery, who have failed or have a contraindication to other treatments, while taking into account comorbidities and after providing information about adverse effects (Level 4, Strength D)	9.1 \pm 1.5
6. Intra-articular corticosteroid injections can be proposed (Level 1A, Strength A), especially for inflammatory flare-ups with joint effusion (Level 4, Strength D)	9.7 \pm 0.7
7. Intra-articular hyaluronic acid injections can be proposed (Level 1A, Strength A) without expecting a chondroprotective effect (Level 1B, Strength B)	9.1 \pm 1.5

8. Symptomatic slow-acting drugs in osteoarthritis (avocado and soybean unsaponifiables, chondroitin, glucosamine, diacerein) can be proposed (Level 1A, Strength A) without expecting a chondroprotective effect (Level 1A, Strength A)	8.7 ± 1.4
9. Low-dose topical capsaicin (< 1%) can be considered (Level 1A, Strength C)	8.2 ± 1.8
10. Off-label duloxetine can be considered in the absence of therapeutic alternatives (Level 1A, Strength C)	8.2 ± 1.9
11. No conclusions could be made on the benefits of intra-articular injections of platelet concentrates given the lack of follow-up and insufficient data (Level N/A, Strength N/A)	8.2 ± 2.4

N/A: not applicable, NSAIDs: non-steroidal anti-inflammatory drugs, PRP: platelet-rich plasma

Table 2. Level of agreement – review committee

	Mean ± SD
Principles	
A – non-pharmacological	9.8 ± 0.8
B – personalized	9.3 ± 1.2
C – symptomatic and functional	8.2 ± 1.9
D – regular re-assessment	9.2 ± 1.4
E – arthroplasty	9.6 ± 0.9
Recommendations	
1 – paracetamol	8.5 ± 2.2
2 – oral NSAIDs	8.2 ± 2.1
3 – topical NSAIDs	6.8 ± 2.8
4 – weak opioids	8.3 ± 1.7
5 – strong opioids	6.8 ± 2.6
6 – intra-articular corticosteroids	7.5 ± 2.3
7 – intra-articular hyaluronic acid	8.4 ± 2.1
8 – slow-acting drugs in osteoarthritis	7.2 ± 3.0
9 – topical capsaicin < 1%	5.3 ± 2.6
10 – duloxetine	3.1 ± 2.7
11 – platelet-rich plasma	8.7 ± 1.7