The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis is applicable to Russian clinical practice: A consensus statement of leading Russian and ESCEO osteoarthritis experts

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The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) treatment algorithm for the management of knee osteoarthritis (OA), published in December 2014, provides practical guidance for the prioritization of interventions. This current paper represents an assessment and endorsement of the algorithm by Russian experts in OA for use in Russian clinical practice, with the aim of providing easy-to-follow advice on how to establish a treatment flow in patients with knee OA, in support of the clinicians' individualized assessment of the patient. Medications recommended by the ESCEO algorithm are available in Russia. In step 1, background maintenance therapy with symptomatic slow-acting drugs for osteoarthritis (SYSADOA) is advised, for which high-quality evidence is provided only for the formulations of patented crystalline glucosamine sulphate (pCGS) (Rottapharm/Meda) and prescription chondroitin sulfate. Paracetamol may be added for rescue analgesia only, due to limited efficacy and increasing safety signals. Topical non-steroidal anti-inflammatory drugs (NSAIDs) may provide additional symptomatic treatment with the same degree of efficacy as oral NSAIDs but without the systemic safety concerns. To be effective, topical NSAIDs must have high bioavailability, and among NSAIDs molecules like etofenamate have high absorption and bioavailability alongside evidence for accumulation in synovial tissues. Oral NSAIDs maintain a central role in step 2 advanced management of persistent symptoms. However, oral NSAIDs are highly heterogeneous in terms of gastrointestinal and cardiovascular safety profile, and patient stratification with careful treatment selection is advocated to maximize the risk: benefit ratio. Intra-articular hyaluronic acid as a next step provides sustained clinical benefit with effects lasting up to 6 months after a short-course of weekly injections. As a last step before surgery, the slow titration of sustained-release tramadol, a weak opioid, affords sustained analgesia with improved tolerability.

Key words: hyaluronic acid; non-steroidal anti-inflammatory drugs; patented crystalline glucosamine sulfate; knee osteoarthritis; symptomatic slow-acting drugs for osteoarthritis.

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Introduction

Osteoarthritis (OA) is the most common form of arthritis and a major cause of disability. Over 4 million people in Russia have an established diagnosis of OA [1, 2]; however, extrapolation of epidemiological data investigating the prevalence of OA in a study cohort suggests that the number of people living with OA may be closer to 15 million people in the general population [3]. OA affects more than 20 per 1000 people aged 18 and over in Russia, while the primary disease incidence exceeds 5 per 1000 adult population. The incidence of OA in Russia is rising steadily, with around 600,000 new cases of OA registered in Russia annually. The most common localization of OA is the knee joint. In the Kursk region of Russia alone, with a population of 1.2 million, symptomatic knee OA affects 25% of the population aged between 38 to 95 years old. Over 50% of OA patients are elderly with limited physical ability [2], and with frequent comorbidities, commonly arterial hypertension, diabetes mellitus and ischemic heart disease.

Treatment guidelines recommend structural joint protection alongside pain relief to control OA disease activity and improve quality of life [4]. While multiple national and international guidelines for OA exist, which analyze the level of evidence behind each intervention, few

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recommendations prioritize the interventions in a given sequence [5–8]. In 2014, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) published a treatment algorithm for the management of knee OA which provides practical guidance for the prioritization of interventions and guides physicians through progressive, logical steps [4].

A workshop was held between members of the international ESCEO task force (O.B., C.C., and J.-Y.R.) and a group of Russian orthopaedic surgeons and rheumatologists during the ESCEO Congress, in Malaga, Spain on 14 April 2016, with the aim of reviewing the ESCEO treatment algorithm for knee OA and assessing the applicability of the algorithm to the Russian situation. The Russian consensus group were in general agreement that the principles of the ESCEO algorithm were applicable to the management of knee OA in Russia, and provided their endorsement for the algorithm to be recommended to rheumatologists and orthopaedic surgeons across Russia to follow. Specific details of the stepwise algorithm, as endorsed by this Russian consensus group, are reviewed in this paper.

Step 1: Pharmacological treatment

The ESCEO treatment algorithm for knee OA recommends background pharmacological therapy if the patient is still symptomatic, in parallel to non-pharmacological management which was beyond the scope of discussion. The stepwise, sequential structure outlined in **Figure 1** proposes that the patient is progressively moved along the algorithm as soon as the clinical response is not satisfactory.

Paracetamol

Paracetamol has been widely recommended as a first-line step for rescue analgesia, even though the effect of paracetamol on symptoms is minimal with only a small effect size (ES) on pain at 0.14 (95% confidence interval [CI] 0.05 to 0.22) and no significant effect on stiffness and physical function in patients with knee OA [9, 10]. The persistent use of paracetamol is largely due to the presumed safety of paracetamol and low cost; however, there are recent concerns over the safety profile of paracetamol. A systematic review has identified a striking dose-response trend between paracetamol at standard analgesic doses (0.5–4.0 g/day) and adverse events (AEs) including: increased mortality, cardiovascular (CV), gastrointestinal (GI) and renal AEs in the general population [11]. For these reasons, the ESCEO task force preferentially recommends symptomatic slow-acting drugs for osteoarthritis (SYSADOA) first line for knee OA with paracetamol only as short-term rescue analgesia as needed in addition to SYSADOA therapy (Figure 1) [4].

SYSADOAs

The preferred approach to Step 1 treatment of knee OA recommended in the ESCEO algorithm and advocated by this consensus group is to initiate background therapy with chronic SYSADOA [4]. Among SYSADOAs, the evidence is greatest for the effect of prescription-grade glucosamine sulfate (GS) and chondroitin 4&6 sulfate (CS). Although the ES of CS on pain is reportedly variable [7], CS may offer some benefit on joint structure changes in patients with mild to moderate OA in the long term [12]. Other SYSADOAs, including diacerein, avocado-soybean unsaponifiable (ASU), collagen fragments or plants extracts have been suggested as potential treatments for OA, although the evidence for any preclinical or clinical effect is limited [13–15]. Diacerein may offer a small symptomatic benefit with prolonged pain reduction, albeit with diarrhoea frequently reported as the most common AE [16, 17].

Numerous formulations of glucosamine as both sulfate (GS) and hydrochloride (GH) salts are available as prescription-only, generic, over-the-counter products and dietary supplements. However, it is apparent from careful consideration of the evidence base that only the patented crystalline glucosamine sulphate (pCGS) formulation (Rottapharm/Meda) [18] has proven efficacy in the treatment of OA [19–21]. Only the pCGS formulation of glucosamine is consistently demonstrated in clinical trials to be effective on OA symptoms including pain and function, and proven to prevent joint structural changes, while no other glucosamine formulation has been shown to be effective [19–23]. The formulation of glucosamine used in practice is critical to the clinical outcomes achieved in OA and for that reason further discussion of glucosamine formulation is given in this article.

Glucosamine and CS are often used in combination as dietary supplements; however, there is only limited evidence to suggest an additional benefit of the combination [24–27]. The combination of GH with CS is most frequently studied, notably in the GAIT study (Glucosamine/Chondroitin Arthritis Intervention Trial) which failed to show a symptomatic effect of the combination in patients with moderate-severe knee pain [24]. The lack of efficacy observed in combination studies may be explained by an observed pharmacokinetic interaction. GH administered at a dosage of 500 mg tid (tablet form) reaches only 50% of the peak plasma levels of pCGS (1500 mg od in liquid form) at steady state, and combination of GH with CS (400 mg tid) significantly decreases the glucosamine bioavailability by a further 25% [28, 29].

Glucosamine sulfate

This consensus group advocates the differentiation of pCGS from other glucosamine preparations as a first-line SYSADOA for medium to

long-term control of knee OA symptoms (Figure 1). Only pCGS is given as a highly bioavailable once-daily dose (1500 mg od) with a proven pharmacological effect [29] that equates to a clear clinical benefit in trials and real-life studies of knee OA [19, 30].

Pharmacokinetics

Pharmacokinetic studies demonstrate that a once daily dose of pCGS at 1500 mg leads to mean plasma concentration at steady state of 9 μM of glucosamine in healthy volunteers [31], while administration of GH (500 mg tid) leads to steady state levels of only 1.2 μM **(Table 1)** [32]. Importantly, in OA patients peak glucosamine concentrations at 7.17 μM (range 3.35 to 22.7) in the plasma and 4.34 μM (range 3.22 to 18.1) in the synovial fluid have been measured after once-daily administration of pCGS (1500 mg) [31, 33]. Mechanistic studies support the role of pCGS as both a symptom- and structure-modifying agent in OA, via glucosamine-induced reversal of the pro-inflammatory and joint-degenerating effects of interleukin-1 (IL-1). Specifically, pCGS inhibits IL-1-induced expression of genes involved in the pathophysiology of joint inflammation and tissue destruction at the optimal plasma concentration of around 10 μM [34].

Efficacy on OA symptoms

A Cochrane review of 25 randomized controlled trials of all glucosamine formulations in 4,963 OA patients, concluded that *«only those studies evaluating the Rotta preparation showed that glucosamine was superior to placebo in the treatment of pain and functional impairment»* [19]. Overall, the meta-analysis failed to show any benefit of glucosamine for pain (standardized mean difference [SMD] -0.16; 95% confidence interval [CI] -0.36 to 0.04). Separate analysis of trials using any non-pCGS preparation of glucosamine also failed to show any benefit over placebo for pain (SMD -0.05; 95% CI -0.15 to 0.05). Conversely, analysis of trials found pCGS to be superior for pain (SMD -1.11; 95% CI -1.66 to -0.57) and function (Lesquesne index SMD -0.47; 95% CI -0.82 to -0.12) [19]. The superiority of the pCGS formulation is confirmed by analysis of the 3 high quality (Jadad score 5), «low risk of bias» trials of pCGS [22, 23, 35], for which the calculated global ES of pCGS on pain was 0.27 (95% CI 0.12 to 0.43) [20, 21].

Although the ES measured for pCGS is moderate, it is greater than the effect of paracetamol (ES 0.14) as confirmed in a head-to-head study [35], and similar to the ES measured for non-steroidal anti-inflammatory drugs (NSAIDs) (ES 0.32; 95% CI 0.24 to 0.39) [9, 36]. In addition, a significant effect on function for pCGS was shown with an ES of 0.33 (95% CI 0.17 to 0.48) for Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) function and 0.38 (0.18 to 0.57) for Lesquesne index [20].

Efficacy on disease-modifying effects

Long-term studies demonstrate a significant reduction in joint space narrowing (JSN) with pCGS as compared with placebo over 3 years of treatment [22, 23]. A lack of progression of JSN over 2–3 years (determined at a threshold of

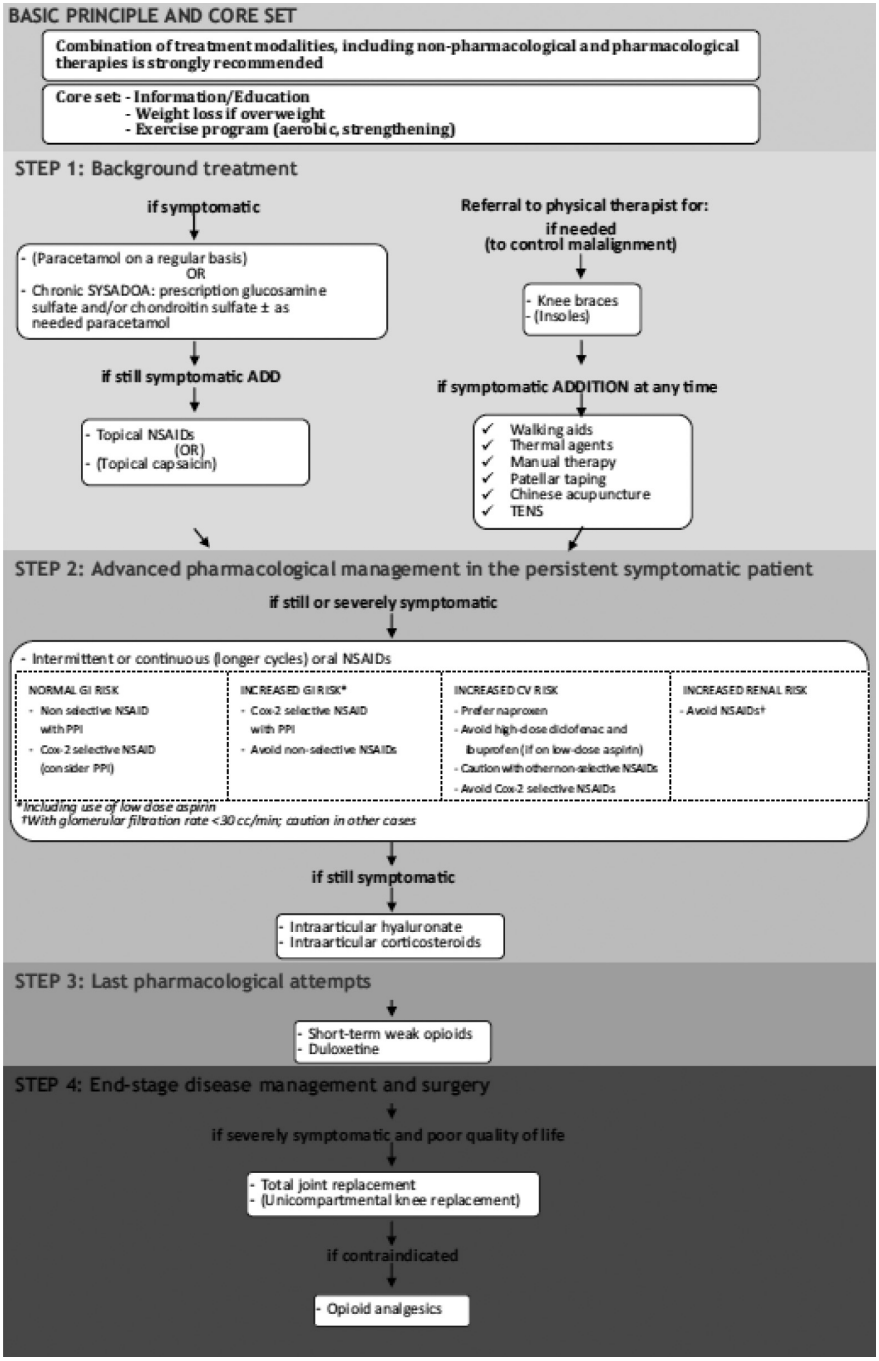

Figure 1: Knee osteoarthritis treatment algorithm [4]. *Including use of low dose aspirin. †With glomerular filtration rate <30 cc/min; caution in other cases. COX-2, cyclooxygenase-2; CS, chondroitin sulfate; CV, cardiovascular; GI, gastrointestinal; IA, intra-articular; NSAID, non-steroidal anti-inflammatory drug; pCGS, patented crystalline glucosamine sulfate; PPI, proton pump inhibitor; SYSADOA, symptomatic slow-acting drugs in osteoarthritis; OA, osteoarthritis.

Table 1 Pharmacokinetic parameters for patented crystalline glucosamine sulfate (pCGS) (1500 mg qd) and glucosamine hydrochloride (1500 mg qd or 500 mg tid). Adapted from Persiani et al. 2005 [31] and Jackson et al. 2010 [32]

	pCGS 1500 mg qd	GH 1500 mg qd	GH 500 mg tid
	Steady state	Single dose	Steady state
C_{max} (mean)			
ng/mL	1,602±425	492±161	211±93
μM	8.9±2.4	2.7±0.9	1.2±0.5
$T_{1/2}$ (hours)	15	2.51±1.84	3.94±2.41

qd, once daily; tid, three times daily; GH, glucosamine hydrochloride; pCGS, patented crystalline glucosamine sulfate.

0.5 mm [>0.3–0.7 mm]) has demonstrated predictive value of >90% for not having joint replacement surgery [37], and is proposed as a surrogate marker for total joint replacement (TJR) [38]. The proportion of patients with severe JSN of >0.5 mm was significantly reduced in both pCGS pivotal 3-year trials: by one-half (15% vs. 30% with placebo; p=0.013) [22] to two-thirds (5% vs. 14% with placebo; p=0.05) [23]. Over the 3 years of treatment, there was a progressive loss of JSW with placebo, which was not observed with pCGS **(Table 2)** [22, 23]. Furthermore, treatment with pCGS for at least 12 months significantly delayed the need for joint surgery (p=0.026); TJR occurred in twice as many patients from the placebo group in the 5 years of follow-up compared with those patients who had received pCGS (relative risk [RR] 0.43; 95% CI 0.20 to 0.92) [30].

Russian real-life studies

Real life studies conducted in Russia confirm the results derived from controlled clinical trials. In Russia, pCGS may be given as a course of 3 intramuscular (im) injections per week for one month (400 mg), followed by oral formulation at 1500 mg/once daily. The relative bioavailability of glucosamine following im injection is 93%, while after oral administration the bioavailability is 44% due to first-pass metabolism in the liver [39]. Among patients with knee OA of radiological stage I to III (n=155) treated with im pCGS (400 mg twice-weekly) or placebo in a randomized trial, 50% of patients responded to pCGS treatment after 6 weeks (⩾3 point reduction in Lesquesne index); this was a significantly higher responder rate than observed with placebo (51% vs. 30%, respectively; p=0.015) [40]. In real-life studies, treatment with pCGS using the im (three-times weekly) for one month followed by oral administration protocol has demonstrated a close to 50% reduction in patient-reported pain on a visual analogue scale (VAS 0–100; reduction from 95 to 54 mm), and allowed some patients the freedom to resume physical activities (e.g. Nordic walking) (Prof. Knyazeva, personal communication).

An open study comparing different pharmacotherapies for OA was conducted in Russia. Eighty OA patients were randomized to 1 of 4 treatment arms including: paracetamol (up to 2 g/day), pCGS (1500 mg/day), CS (1000–1500 mg/day) and meloxicam (7.5–15 mg/day) for 18 months [41]. The proportion of OMERACT-OARSI treatment responders was highest in the meloxicam group (100%), 90% in the pCGS and CS groups and 75% in the paracetamol group. Mean JSN measured at the study end was significantly lower for the pCGS (-0.07; p=0.0002), CS (-0.1; p=0.004) and meloxicam (-0.06; p=0.006) groups compared with placebo (-0.37). In addition, the proportion of patients without severe JSN (⩾0.5 mm in the medial knee joint) was lowest for pCGS compared with the other 3 treatments **(Figure 2)** [41].

Pharmacoeconomics

The pharmacoeconomic benefits of long-term pCGS are demonstrated in real-life studies showing a reduction in need for concomitant analgesia and NSAID use of 36–50% [30, 42], and in reduction of the utilization of healthcare resources, including physician visits and examinations **(Table 3)** [30]. Cost-effective analysis of a 6-month treatment trial using the incremental cost-effectiveness ratio shows pCGS to be a highly cost-effective therapy for treatment of patients with primary knee OA compared with paracetamol and placebo [35, 43]. Furthermore, pCGS may be taken safely in the long term with an AE rate comparable with placebo [19, 22, 23, 35]. The CV safety of pCGS is also demonstrated in the long term, even in patients with OA with concomitant hypertension, hypercholesterolemia or hyperglycemia [44].

In conclusion, only the pCGS preparation of glucosamine is recommended as first line therapy for knee OA management.

Topical NSAIDs

Topical NSAIDs may be added to the treatment regimen if the patient is still symptomatic after appropriate background pharmacological therapy with SYSADOAs, and rescue analgesia with paracetamol provides insufficient symptom relief. The efficacy of topical NSAIDs in knee OA has been established in randomized trials and meta-analyses [45–48]. A trial conduced in

Table 2 Prevention of joint space narrowing in knee osteoarthritis with patented crystalline glucosamine sulfate (pCGS) over 3 years' treatment. Adapted from Reginster et al. 2001 [22] and Pavelka et al. 2002 [23]

Reginster et al. 2001 [22]	Placebo (n=106)	pCGS (n=106)	Difference	P value
JSW at enrolment, mm (mean±SD)	3.95±1.24	3.82±1.32	–	–
3-year JSN, mm (mean and 95% CI)	-0.40 (-0.56 to -0.24)	-0.07 (-0.22 to 0.07)	0.33 (0.12 to 0.54)	0.003
Pavelka et al. 2002 [23]	**Placebo (n=101)**	**pCGS (n=101)**	**Difference**	**P value**
JSW at enrolment, mm (mean±SD)	3.63±1.57	3.89±1.48	–	–
3-year JSN, mm (mean and 95% CI)	-0.19 (-0.29 to -0.09)	0.04 (-0.06 to 0.14)	0.23 (0.09 to 0.37)	0.001

CI, confidence interval; JSN, joint space narrowing; JSW, joint space width; pCGS, patented crystalline glucosamine sulfate; SD, standard deviation.

Russia and the Ukraine investigated the treatment of knee OA in 4,931 patients using either SYSADOA monotherapy (pCGS) or a combination of SYSADOA (pCGS) plus a topical NSAID (diclofenac gel or aescine gel) for 8 weeks [49]. Patients assigned combination treatment received either diclofenac gel (Russian patients) or aescine gel (Ukranian patients) 2–3 times a day on the affected joint and pCGS (3 times/week im) and pCGS (1500 mg/day per os). The study found that greater reduction in pain was achieved with the combination treatment on a VAS and WOMAC scale, and the pain reduction occurred 3 weeks earlier compared with monotherapy. A gradual reduction in pain intensity across the whole 8 week study was observed and overall pain levels reduced from severe pain (0.6–1.0 at the study start to mild pain (0.2) by study end for both combination treatment groups **(Figure 3)**.

Topical NSAIDs such as etofenamate are as effective as oral NSAIDs [50], but with a lower risk for GI AEs albeit with an increased risk of mild skin reactions [45, 51]. The pooled ES for pain relief with topical NSAIDs is 0.44 (95% CI 0.27 to 0.62), although there are some differences between products (I^2=69%) [46]. Topical NSAIDs are recommended earlier than oral NSAIDs due to their lower systemic absorption and better tolerability profile, and may be the preferred treatment option, particularly in OA patients aged ⩾75 years, and those with co-morbidities or at an increased risk of GI, CV or renal side effects.

Choice of topical NSAID may be important, as good absorption through the skin and accumulation of the active agent in the target tissues are important factors which contribute to efficacy, alongside low plasma levels to minimize systemic AEs and improve tolerability. The bioavailability of topical NSAID formulations varies, with etofenamate demonstrating the highest bioavailability at 21% [52], and accumulation in inflamed target tissues at levels 10-times the plasma concentration [53].

Step 2: Advanced pharmacological treatment

Oral NSAIDs

If Step 1 treatments show inadequate efficacy, or in patients presenting with moderate-severe pain, benefit may be obtained with advanced pharmacological treatments, including oral NSAIDs. Oral NSAIDs have a moderate effect on pain relief, with ES 0.29 (95% CI 0.22 to 0.35) that is greater than that of paracetamol (ES 0.14) [9], and with greater efficacy in patients with more severe OA [54]. Cyclo-oxygenase-2 (COX-2) selective, partially-selective, or non-selective NSAIDs are similarly effective in controlling pain [45]. However, there are vast differences between individual drugs in terms of benefit-risk balance, which is mainly driven by their GI and CV safety profile.

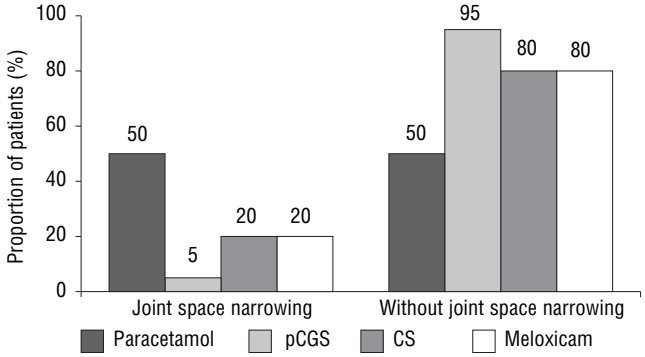

Figure 2: Proportion of patients (%) with severe joint space narrowing (⩾0.5 mm) in medial part of knee joint after pharmacological treatment with paracetamol (up to 2 g/day), pCGS (1500 mg/day), CS (1000–1500 mg/day) and meloxicam (7.5–15 mg/day) for 18 months. The significance of differences: paracetamol – p <0.00001; for pCGS, CS, and meloxicam – p = 0.02. Adapted from: Tsvetkova et al. 2015 [41].

Appropriate selection of the oral NSAID is important. Oral NSAID treatment is associated with a 3- to 5-fold increased risk of upper GI complications (UGIC) [55, 56]. The high risk of UGIC with indomethacin may be attenuated by use of acemetacin, a prodrug, which is less active on the COX-1 enzyme in the gastric mucosa, resulting in a reduction in GI AEs of around one-third [57]. Acemetacin also demonstrates similar efficacy to celecoxib for knee OA, with a low incidence of AEs [58]. Celecoxib and ibuprofen have a low relative risk for UGIC compared with other NSAIDs [59], while nabumetone is associated with 10-times fewer GI AEs than other NSAIDs [60, 61].

Prior to making treatment decisions, patients should be assessed for risk factors and the risk: benefit ratio of treatment determined. Several patient factors increase the risk of UGIC, including advanced age, a history of GI ulcer, and concomitant treatment with corticosteroids, aspirin or anticoagulants [62, 63]. In patients with low (normal) GI risk, prescription of either a non-selective NSAID with or without a proton pump

Table 3 Use of health resources per patient per year among OA patients who had received patented crystalline glucosamine sulfate (pCGS) formulation 5 years' previously versus placebo. Adapted from Bruyere 2008 [30]

Mean costs, € (US$)†	Placebo (n=43)	pCGS (n=58)
Cost of analgesics	59 (77)	19 (25)
Cost of NSAIDs	116 (151)	63 (82)
Total cost of OA drugs (including analgesics, NSAIDs etc.)	204 (265)	108 (140)
Number of visits to specialist, mean (SE)	2.1 (0.5)	1.8 (0.3)
Number of paramedic visits for OA	17.4 (6.3)	6.6 (2.0)
Number of radiographs for OA	0.60 (0.14)	0.44 (0.09)
Number of gastroscopies	0.30 (0.07)	0.10 (0.04)
Total cost calculated for OA-related resources††	605 (786)	292 (380)*

† 1 € (euro) = approx. 1.3 US$ (2007); ††Total cost calculation includes costs of secondary healthcare visits (paramedic, specialist), examinations (radiographs, gastroscopies) and medication costs (analgesics, NSAIDs etc.); * p=0.024 vs. placebo. NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; pCGS, patented crystalline glucosamine sulfate.

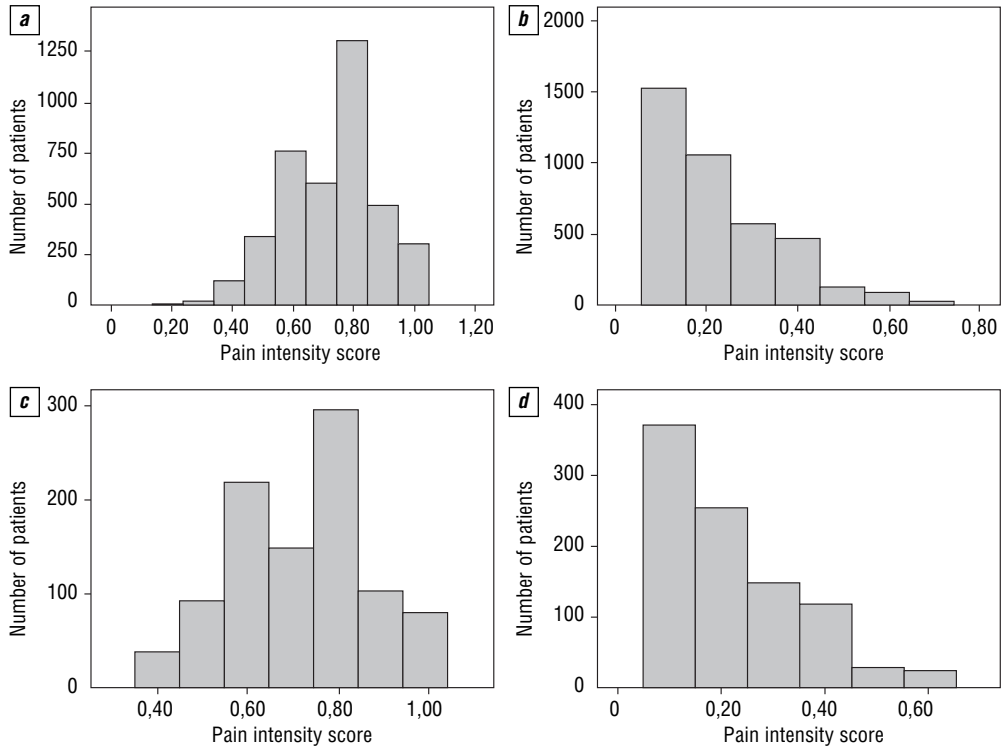

Figure 3: Pain intensity at baseline a) and b) after 8 weeks combined therapy with diclofenac gel and patented crystalline glucosamine sulfate (pCGS) (im and per os); and at baseline c) and d) after 8 weeks combined therapy with aescine gel and pCGS im and per os. Adapted from Tsvetkova 2004 [49].

inhibitor (PPI) or a COX-2 selective NSAID should be considered based on the clinician's judgement (Figure 1) [4]. In patients with high GI risk, which includes patients receiving concomitant low-dose aspirin, non-selective NSAIDs should be avoided and COX-2 selective NSAIDs should be co-prescribed with a PPI [64].

All oral NSAIDs increase the risk of serious CV events [65] and should be avoided in high CV risk patients. Naproxen is the exception, and may be used if an NSAID is required in patients at high CV risk [65, 66]. Oral NSAID use should be avoided in patients with increased renal risk, such as chronic kidney disease with estimated glomerular filtration rate <30 cc/min [4].

The consensus group recommends that all NSAIDs are used at the lowest effective dose for the shortest period of time necessary to control symptoms, either intermittently or continuously in longer cycles (1). In the event of insufficient control of symptoms, the combination of NSAIDs is not recommended as there is no evidence of additional benefit, and an increased risk of AEs, with additional cost of treatment. While switching NSAIDs may provide some benefit, the consensus group does not recommend multiple successive rounds of NSAIDs before considering other treatment options. In the case of contraindications to NSAIDs, or if the patient is still symptomatic despite use of NSAIDs, intra-articular treatment may be considered (Figure 1).

Hyaluronic acid

Viscosupplementation with intra-articular (IA) hyaluronic acid (HA) is an effective treatment for knee OA with beneficial effects on pain, function and patient global assessment [67]. Furthermore, IA HA may delay the need for total knee replacement (TKR) surgery by approximately 2 years [68–70]. HA has an ES of 0.63 when compared with oral placebo [71]. The IA delivery method itself has a significant ES of 0.29; despite this, a statistically significant ES on pain at 3 months of 0.34 (95% credible interval [CrI] 0.26 to 0.42) was shown for IA HA [71]. The ES of IA HA on pain is not significantly different to that of NSAIDs given for up to 12 weeks [72], but IA HA demonstrates a more favourable safety profile, with injection site pain as the most common AE. As such, IA HA may be a good alternative to NSAIDs for knee OA, especially for older patients or in those at greater risk for NSAID-induced AEs.

HA is not a rapidly acting agent, but has a significant, long-lasting treatment effect extending from 4 weeks up to 26 weeks for knee pain and knee function compared with placebo ($p<0.001$) [73, 74]. IA corticosteroids provide greater pain relief in the short-term up to 4 weeks, while beyond 8 weeks post-injection IA HA demonstrates superior, longer-lasting efficacy [75]. Most head-to-head clinical trials have found no difference in symptomatic efficacy between the HA preparations of various molecular weights (MWs) [76–80]. However, cross-linked high MW HAs (hylans) are twice as likely to cause local adverse reactions (RR 1.91; 95% CI 1.04 to 3.49and flares (RR 2.04; 95% CI 1.18 to 3.53) compared with intermediate or low MW HA [81].

It is proposed that the mechanism of action of exogenous HA can occur in 2 stages: a mechanical stage and a pharmacological stage [75, 82]. Injection of HA provides viscosupplementation [83, 84] and can induce biosynthesis of endogenous HA and extracellular matrix components [85], a process that is influenced by the concentration and MW of the HA [85, 86]. The optimal stimulation of HA biosynthesis occurs with intermediate MW HA binding to synovial fibroblast cell receptors; this binding may be limited by the steric volume of high MW HA, and only weak binding occurs with low MW HA [85]. In

one large trial of intermediate MW HA (Go-On®, Rottapharm/Meda) versus low MW HA (Hyalgan®, Fidia Pharma), the intermediate MW HA provided statistically superior pain relief at 6 months (p=0.021) [87], a difference that might be explained by the additional effect of stimulation of endogenous HA production. The symptomatic action of the intermediate MW HA (Go-On) is confirmed in a small study of 20 patients with knee arthrosis (at the Rostov-on-Don Municipal Hospital), finding that a 5-week course of HA injection led to a sustained reduction in pain intensity and improvement in knee joint function for at least 16 weeks following treatment, with no systemic reactions or complications reported [88].

While further investigation into the OA patient types most likely to benefit from IA HA is warranted, the consensus group recommends the use of IA HA in knee OA patients with mild-moderate disease, and for more severe patients who are either contraindicated to TKR or wishing to delay surgery. IA HA should only be administered in knee OA once the acute inflammatory flare has settled. In these patients, IA corticosteroids may be used first line to treat the knee effusion.

Step 3: Last pharmacological treatment

Last pharmacological options for the severely symptomatic patient are represented by the use of short-term weak opioids, such as tramadol. Antidepressants, including duloxetine, have been used in chronic pain syndromes because they act centrally to alter pain neurotransmitters (serotonin and norepinephrine) although scant evidence of an effect is shown in OA with a high rate of AEs [89, 90]. Tramadol and duloxetine should not be used in combination, due to the overlapping actions on central pain neurotransmitters.

Tramadol

Tramadol is a synthetic, centrally-acting opioid agonist that acts through both weak opioid and non-opioid mechanisms [91]. Consequently, tramadol rarely causes the AEs commonly associated with conventional opioid drugs. The most frequently reported AEs with tramadol are nausea and headache, which may result in treatment withdrawal and suboptimal pain management [92, 93]. There is good evidence that short-term tramadol works for severely symptomatic OA patients if prescribed properly. Treatment of knee OA with short-term tramadol reduces pain and stiffness and improves function and overall well-being, with significant results for patients' overall assessment of therapy compared with placebo [94, 95].

The sustained release (SR) formulation of tramadol is preferred as it is associated with fewer side effects [96]. The multi-unit micropellet SR capsule formulation of tramadol (Meda) delivers prolonged effective plasma levels of tramadol with low variability in terms of both rate and extent of absorption [97], thus preventing the high plasma peaks associated with AEs found with the immediate-release formulations [96, 97]. Furthermore, the slow upwards titration of tramadol SR from 50 mg up to 100 mg bid over 7 days is recommended to improve tolerability and minimize treatment discontinuations due to AEs [98].

Step 4: End-stage disease management and surgery

Full review and advice on surgical procedures for the management of end-stage knee OA is beyond the scope of this consensus statement. TJR is cost-effective when all previous modalities have failed and there is significant loss in quality of life [99]. TJR is very effective in relieving severe symptoms of knee OA and has a high benefit: risk ratio when patients are carefully selected [8]. Unicompartmental knee replacement may be effective when the disease is restricted to a single knee joint compartment [100]; however, it is associated with a higher revision rate than total knee arthroplasty [101].

Different methods to repair cartilage defects and unload joint surfaces at early stages of arthrosis have been developed [102]; however, there is a lack of quality supporting evidence [103]. Currently, no evidence suggests differences between different osteotomy techniques [104], and there is insufficient evidence from randomized trials to determine which interventions are best for osteochondral defects [105]. Long-term data suggest that joint function may improve after some types of autologous chondrocyte implantation (ACI) [106, 107].

Studies conducted in Russia have examined the use of postoperative treatment on functional recovery after non-destructive surgery for knee OA (at the Rostov-on-Don Municipal Hospital) [108, 109]. Mosaic autochondroplasty was conducted on patients with knee OA (n=96; Kellgren-Lawrence 2–3 and local cartilage defects Outerbridge 3–4), which has demonstrated effectiveness for restoration of limited defects on an articulate surface. Following mosaicplasty (MP) surgery, patients could receive pCGS therapy for 2 years or control (symptomatic NSAIDs). Use of pCGS in the postoperative period had positive slow-acting structural modifying effects on the hyaline cartilage and considerably improved the functional outcome of treatment in the mid-term follow-up (measured by International Knee Documentation Committee [IKDC] knee functional assessment); IKDC average for 2 years was 50.5±4.98 with MP + pCGS and 42.33±6.69 for MP + NSAID.

Finally, for severely symptomatic patients in whom surgery is contraindicated, the last pharmacological option is represented by classical oral or transdermal opioids, although their small to moderate efficacy is outweighed by a large increased risk of AEs [110].

Conclusions

Assessment of the evidence base by an international ESCEO task force has provided, for the first time, a stepwise multi-modal treatment algorithm for the practical management of knee OA (Figure 1) [4]. As a group of Russian rheumatologists and orthopaedic surgeons, we have reviewed the ESCEO algorithm and consider it to be broadly similar to our treatment practice in Russia. Thus, as described in this paper, we endorse the principles of the ESCEO algorithm and have reached a consensus regarding recommendations for the stepwise multi-modal treatment of knee OA in Russia. In clinical practice, treatment should be based upon the individualized assessment of the patient, taking into account patients' needs and preferences, or the subjective interpretation of the evidence by the physician. In the future, identification of patient profiles may lead to more personalized healthcare, with more targeted treatment for OA. For now, this stepwise approach to the pharmacological management of knee OA is advocated by the Russian consensus group.

During step 1, in addition to non-pharmacological background therapy, treatment with SYSADOAs using only the pCGS formulation (Rottapharm/Meda) or prescription CS is recommended, with paracetamol as add-on rescue analgesia for short-term therapy. It is important to note that, while

multiple formulations of glucosamine exist, different effects are obtained with the different formulations. Evidence for symptomatic efficacy is only demonstrated with the pCGS formulation, with ES on pain greater than that of paracetamol and similar to oral NSAIDs, while the ES for other glucosamine formulations is consistently demonstrated to be zero. Thus, only the pCGS formulation is afforded with our recommendation for use in knee OA. Topical NSAIDs may be included for additional analgesia given that their symptomatic efficacy is similar to the oral NSAIDs but with superior systemic safety. To be effective, topical NSAIDs must have high absorption and bioavailability. Etofenamate is recommended due to its high absorption and the highest bioavailability among topical NSAIDs, alongside evidence for accumulation in synovial tissues.

Oral NSAIDs maintain a central role in step 2 advanced pharmacological management of the persistently symptomatic patient. NSAIDs as a class are heterogeneous and there is wide disparity in the AE risk for GI and CV events between different oral NSAIDs. Among oral NSAIDs, acemetacin and nabumetone may be recommended due to their comparable efficacy with low propensity to cause AEs. Patient stratification and careful selection of appropriate medication can help to minimize risks while maintaining clinical benefit of treatment. Intra-articular treatment represents the next stage in the algorithm, for patients who fail to derive sufficient symptomatic benefit from prior treatments. IA HA can be clearly differentiated from IA corticosteroids by the duration of the induced benefit, lasting for up to 6 months after a short weekly injection course. There is some evidence that choice of IA HA product may affect the magnitude of clinical effect derived. As well as providing viscosupplementation, intermediate MW HA has the propensity to induce the biosynthesis of HA and has shown superior efficacy to low MW HA, with less associated AEs than the cross-linked, high MW HAs.

Step 3 comprises the last pharmacological attempt before surgery and includes short-term weak opioids, such as tramadol. SR formulation using a multipellet technology and dose titration of tramadol can help to limit the side effects often associated with opioid treatment, and minimize treatment discontinuations while providing sustained efficacy. Overall, this guidance provides evidence-based and easy-to-follow advice on how to establish a treatment flow in patients with knee OA, for practical implementation in Russian clinical practice.

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