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Efficacy and safety of glucosamine sulfate in the management of osteoarthritis: Evidence from real-life setting trials and surveys

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ABSTRACT

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) treatment algorithm recommends chronic symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) including glucosamine sulfate (GS) and chondroitin sulfate (CS) as first-line therapy for knee osteoarthritis (OA). Numerous studies are published on the use of SYSADOAs in OA; however, the efficacy of this class is still called into question largely due to the regulatory status, labeling and availability of these medications which differ substantially across the world. Examination of the evidence for the prescription patented crystalline GS (pCGS) formulation at a dose of 1500 mg once-daily demonstrates superiority over other GS and glucosamine hydrochloride (GH) formulations and dosage regimens. Thus, the ESCEO task force advocates differentiation of prescription pCGS over other glucosamine preparations. Long-term clinical trials and real-life studies show that pCGS may delay joint structural changes, suggesting potential benefit beyond symptom control when used early in the management of knee OA. Real-life pharmacoeconomic studies demonstrate a long-term reduction in the need for additional pain analgesia and non-steroidal anti-inflammatory drugs (NSAIDs) with pCGS, with a significant reduction of over 50% in costs associated with medications, healthcare consultations and examinations over 12 months. Furthermore, treatment with pCGS for at least 12 months leads to a reduction in the need for total joint replacement for at least 5 years following treatment cessation. Thus, pCGS (1500 mg od) is a logical choice to maximize clinical benefit in OA patients, with demonstrated medium-term control of pain and lasting impact on disease progression.

Introduction

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for management of knee osteoarthritis (OA) recommends the chronic use of symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), in particular prescription glucosamine sulfate (GS) and chondroitin sulfate (CS), as a first-line pharmacological treatment for slow-onset medium to long term control of symptoms [1].

There have been many studies published on the use of SYSADOAs in OA; however, the efficacy of this class still meets with controversy due, in large part to differing regulatory status, labeling and availability of these medications in separate countries and regions of the world [2]. Glucosamine, in particular, is available as prescription patented crystalline glucosamine sulfate (pCGS) formulation (Rottapharm) [3], generic and over-the-counter (OTC) formulations of GS and food supplements mostly containing the glucosamine hydrochloride (GH) salt. Glucosamine supplements vary substantially from the prescription pCGS in their molecular formulation and dose regimens; only prescription pCGS is administered as a highly bioavailable once-daily dose (1500 mg) with a documented pharmacological effect [4]. The ESCEO task force acknowledges the variance in efficacy demonstrated with various glucosamine formulations in clinical studies, and recommends that prescription pCGS should be differentiated from other glucosamine formulations [1,5].

Other international evidence-based guidelines for OA management differ in their recommendations for the use of SYSADOAs [6–9]. Guidelines from the European League Against Rheumatism (EULAR) recommend both GS and CS for symptomatic treatment of

Abbreviations: CS, chondroitin 4&6 sulfate; GH, glucosamine hydrochloride; GS, glucosamine sulfate; pCGS, patented crystalline glucosamine sulfate; SYSADOAs, symptomatic slow-acting drugs for osteoarthritis.

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OA in the European prescription environment, based upon a high level of evidence (1A) [6]. Conversely, the 2012 American College of Rheumatology (ACR) does not recommend GS or CS for knee OA [7], and the 2014 Osteoarthritis Research Society International (OARSI) guideline update gives SYSADOAs an "uncertain" status for pain control [9]. The rationale for these unfavorable and non-committal recommendations may be based upon the lack of availability of prescription medications in the USA, an apparent lack of significant effect on pain when all formulations and trials are pooled in meta-analyses, and the negative results of the National Institutes of Health (NIH)-supported trial of U.S. nutritional supplements including GH [Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT)] [2,10]. Overall, there is consensus across the guidelines to consider that GH is deprived of any benefit for symptomatic knee OA treatment. In guidelines and meta-analyses that separately assess the various formulations of glucosamine, pooled results from studies using any non-pCGS preparation fail to show benefit on pain and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function, while pCGS is consistently rated as providing a greater benefit than placebo or active comparators such as paracetamol in the treatment of pain and functional impairment resulting from symptomatic OA [11].

Mechanism of action of glucosamine

Glucosamine is a natural constituent of glycosaminoglycans in the cartilage matrix and synovial fluid, which when administered exogenously, exerts pharmacological effects on osteoarthritic cartilage and chondrocytes [12–14]. The symptomatic as well as disease-modifying effects attributed to GS may be based upon reports of downregulation in the expression of several inflammatory and degenerative mediators resulting in attenuation of degradation of the cartilage with reduction of disease progression [15]. GS is demonstrated *in vitro* to reduce prostaglandin E2 (PGE2) production and inhibit activation of the nuclear factor kappa B (NFκB) pathway, thus inhibiting the cytokine intracellular signaling cascade in chondrocytes and synovial cells [13,14,16]. In OA, glucosamine induces reversal of the pro-inflammatory and joint-degenerating effects of interleukin-1 (IL-1) [13]. IL-1β is a potent pro-inflammatory cytokine produced in high amounts in the tissues of the OA joint, where it triggers the expression of inflammatory factors such as cyclooxygenase-2 (COX-2), inducible form of nitric oxide (iNOS), IL-6, and tumor necrosis factor-alpha (TNFα). IL-1β also induces cells to produce more IL-1β as well as matrix degradation factors, such as metalloproteinases (MMPs) and a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member TSs (ADAM-TSs). Most of these genes are under the transcriptional control of the signaling pathway nuclear factor NFκB. GS at clinically relevant concentrations reduces COX-2, iNOS, and microsomal prostaglandin E synthase-1 (mPGES-1) gene expression and PGE2 synthesis after IL-1β stimulation, suggesting that glucosamine can control the cascade triggered by inflammatory stimuli [17].

Studies in human chondrocyte cell models demonstrate that pCGS inhibits IL-1-stimulated gene expression of joint degeneration mediators at concentrations in the range of 10 μM, similar to those found in plasma or synovial fluid of knee OA patients after receiving pCGS at the prescription dose (1500 mg od) [15]. pCGS exhibited a dose-dependent effect on IL-1β-induced gene expression of matrix degradation factors MMP-3 (stromelysin-1) and ADAM-TS5 (aggrecanase 2) [15]. Long-term oral administration of GS may reduce the destruction of cartilage and upregulation of MMP-3 mRNA in *in vitro* models [18]. Further, GS is a stronger inhibitor of gene expression than GH, when both are administered at 5 mM doses in a human osteoarthritic explant model [19].

Examination of the evidence base for glucosamine efficacy

Examination of the evidence base for glucosamine identifies that numerous studies of varying quality have been conducted to determine the effect of glucosamine on OA symptoms. A Cochrane review of 25 randomized controlled trials (RCTs) of all glucosamine formulations in 4,963 OA patients, limited to studies with adequate concealment (11 RCTs), failed to show any benefit of glucosamine for pain [standardized mean difference (SMD) = −0.16; 95% confidence interval (CI): −0.36 to 0.04] [11]. However, when the RCTs using the pCGS formulation were analyzed separately, pCGS was found to be superior to placebo for pain (SMD = −1.11; 95% CI: −1.66 to −0.57) and function (Lequesne index SMD = −0.47; 95% CI: −0.82 to −0.12), albeit with high heterogeneity between trials (I^2 = 92%). Conversely, analysis of those RCTs using any non-pCGS preparation of glucosamine failed to demonstrate any benefit over placebo for pain (SMD = −0.05; 95% CI: −0.15 to 0.05) or function (SMD = −0.01; 95% CI: −0.13 to 0.10) [11]. In a meta-analysis of 25 placebo-controlled trials, studies using the pCGS product had a superior outcome on pain in OA compared to other preparations of GS and GH [20].

To address the issue of high heterogeneity that may compound the positive findings for the prescription pCGS formulation, there are three pivotal trials of pCGS that have been judged to be of highest quality using the Jadad quality score for clinical trials [21,22], and independently assessed as the studies with a "low risk of bias" [20]. All three pivotal trials were long-term studies of 6 months to 3 years treatment in patients with mild-moderate pain [20,23–25], for which the calculated global effect size of pCGS on pain was 0.27 (95% CI: 0.12–0.43) without heterogeneity [20,21]. The impact of pCGS formulation on other symptom outcomes was supported by a significant effect size on the WOMAC pain and function subscale scores, and Lequesne algofunctional index; with the absence of heterogeneity (Fig. 1) [21].

While the effect size for pCGS on pain may be considered as moderate at 0.27, it is greater than the effect size reported for paracetamol (0.14; 95% CI: 0.05–0.22) [26], which is recommended as short-term rescue analgesia for OA [1]. Few studies have directly compared pCGS with paracetamol, since paracetamol is often used for rescue analgesia in clinical trials; in one RCT of 6 months treatment, the effect size for pCGS (1500 mg od) on WOMAC pain was 0.25 (95% CI: −0.03 to 0.52) compared with 0.15 (95% CI: −0.12 to 0.42) for paracetamol (3 g/day), demonstrating a trend for superior effect with pCGS although it was not statistically significant [23]. In comparison to non-steroidal anti-inflammatory drugs (NSAIDs), the effect size of pCGS on pain over treatment periods ranging from 6 months to 3 years is equivalent to that achieved with oral NSAIDs, at 0.32 for pain (95% CI: 0.24–0.39) and 0.29 for function (95% CI: 0.18–0.40) for much shorter treatment courses (2–13 weeks) [27,28]. Oral NSAIDs are recommended as step two treatments in persistent symptomatic OA patients [1]. For all treatments, the balance of risk versus benefits must be considered prior to administration. Oral NSAIDs are recommended for short-term use at minimal doses for intermittent or cyclical periods due to concerns over gastrointestinal (GI), renal and cardiovascular adverse events. There is also some epidemiologic evidence for an increased risk of GI adverse events with paracetamol use, including elevation in liver enzymes [26]. Conversely, GS may be taken safely in the long term with an adverse event rate comparable to that of placebo [11].

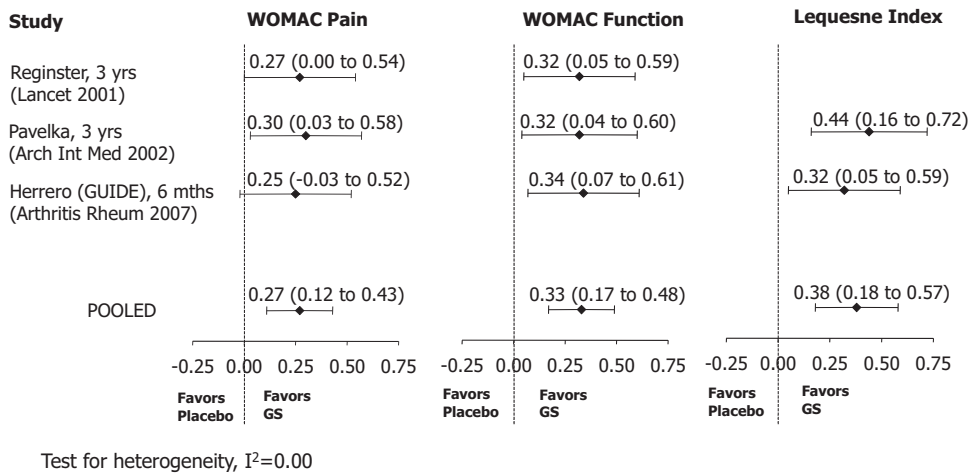

Fig. 1. Effect size (and 95% confidence interval) of patented crystalline glucosamine sulfate (pCGS) (1500 mg od) on knee osteoarthritis symptoms in pivotal trials [21]. (Adapted from Reginster [21].)

Evidence for disease-modifying effects of glucosamine

There is evidence that long-term administration of pCGS may delay joint structure changes, suggesting potential benefit beyond symptom control when used early in the management of OA. Analysis of joint space width (JSW) at trial enrollment and after 3 years of treatment in two RCTs of pCGS versus placebo demonstrated a reduction in joint space narrowing (JSN) with pCGS. In one study, a significant difference in JSN of 0.33 mm (95% CI: 0.12–0.54) was observed with pCGS versus placebo after 3 years ($p = 0.003$) [24]. In the second study, pCGS treatment for 3 years was shown to completely prevent narrowing of the joint (JSN 0.04 mm; 95% CI: −0.06 to 0.14), which was significantly different to the moderate narrowing observed with placebo (−0.19 mm; 95% CI: −0.29 to −0.09; $p = 0.001$) [25] (Table 1). A lack of progression of JSN [determined at a threshold of 0.5 mm (>0.3–0.7 mm)] has demonstrated predictive value of >90% for not having joint replacement surgery [29]. In both studies, fewer patients treated with pCGS experienced predefined severe JSN (>0.5 mm) compared with patients treated with placebo: 15% versus 30% ($p = 0.013$) [24] and 5% versus 14% ($p = 0.05$) [25].

Should glucosamine be combined with chondroitin sulfate?

Long-term studies of prescription chondroitin 4&6 sulfate (CS) have demonstrated that CS may offer similar benefits on joint structure modification in patients with mild-moderate knee OA [30–32]. The effect size of CS on pain reported in meta-analyses ranges from 0.13 (95% CI: 0.00–0.27) to 0.75 (95% CI: 0.50–0.99) [9]; although more current studies show that prescription-grade CS has an effect on joint structural changes with a symptomatic effect that could be clinically relevant [31,33].

Glucosamine and CS are often used in combination as dietary supplements; however, there are no published trials of the combination of the two pharmaceutical-grade prescription preparations. The NIH-sponsored GAIT study described a positive trend for a symptomatic effect of the combination of CS with GH in the subset of patients with moderate-severe pain; this may be considered as effectively CS plus a placebo, as GH alone had no significant effect above the comparator placebo arm [10]. In a similar study, the combination of CS plus GH, the latter being a well-known placebo, had comparable efficacy with celecoxib after 6 months in knee OA patients with moderate-severe pain [34]. Analysis of the Osteoarthritis Initiative (OAI) progression cohort of 600 patients with knee OA found that patients who received the combination of dietary supplement glucosamine and CS had reduced loss of cartilage volume over 2 years, whether or not they were taking concomitant analgesics or NSAIDs [35]. Furthermore, a more recent trial of OA patients reporting chronic knee pain randomized to once-daily non-prescription-grade GS (1500 mg) and CS (800 mg) versus the monotherapies found a statistically significant reduction in JSN at 2 years for the combination compared with placebo (mean difference = 0.10 mm; 95% CI: 0.002–0.20 mm; $p = 0.046$), but no significant structural effect for the single treatment allocations [36]. Thus, there is limited evidence to suggest that combinations of non-prescription-grade glucosamine (including GH) and chondroitin should be preferred to either of the two single, pharmaceutical-grade prescription agents. Conversely, since both prescription pCGS and CS are considered as safe and effective medications, with no difference in adverse events compared with placebo [11,31], it may be wise to perform placebo-controlled RCTs to confirm the clinical benefit of the combination of the two prescription-grade agents beyond monotherapies alone.

Evidence from real life studies and surveys

While clinical trials are important to show if a medication can generate a clinically relevant effect size with good tolerability, RCTs have a number of limitations, particularly as they by necessity screen for a selective patient population. This selectivity of the study population may prevent generalization of the results. Therefore, it would be ideal to test pharmaceuticals in real-life studies, using a non-selected patient population against standard-of-care treatments (and not just in placebo-controlled studies) for clinically relevant endpoints. In a real-life, long-term follow-up of knee OA patients who had participated in the two 3-year trials of pCGS, treatment with pCGS for at least 12 months significantly delayed the need for total joint replacement (TJR) surgery ($p = 0.026$) (Fig. 2) [37]. After a mean follow-up of 5 years after the RCTs, the TJR occurred in over twice as many patients from the placebo group (14.5%) compared with those patients formerly receiving pCGS (6.3%; $p = 0.024$), demonstrating a 57% reduction in risk of TJR with pCGS (relative risk = 0.43; 95% CI: 0.20–0.92) [37]. pCGS is one of the few medications for which this effect has been demonstrated on such a long period of follow-up; fewer patients who received licofelone versus naproxen in a 2-year RCT for knee OA had a TJR during 4–7 year of follow-up, although the difference was not significant [38]. As by definition in all real life studies, there was no standardization of patient's treatment after

Table 1
Evidence for a disease-modifying effect of patented crystalline glucosamine sulfate (pCGS): prevention of joint space narrowing in knee osteoarthritis [24,25]

Reginster et al. [24]	Placebo (n = 106)	pCGS (n = 106)	Difference	p Value
JSW at enrollment, 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 (0.12–0.54)	0.003
Pavelka et al. [25]	**Placebo (n = 101)**	**pCGS (n = 101)**	**Difference**	**p Value**
JSW at enrollment, 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 (0.09–0.37)	0.001

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

the end of the pCGS trial. It is not possible therefore to discriminate whether the treatment received afterwards could have influenced the primary outcome in this study.

Evidence for a reduction in the need for rescue pain analgesia achieved with continuous prescription pCGS is provided by a recent real-life study, representing OA patients in everyday life. The Pharmaco-Epidemiology of GonArthroSis (PEGASus) study was conducted by the French Health Authorities in collaboration with a panel of French rheumatologists and epidemiologists. The primary objective of the study was to assess the impact of SYSADOAs on the use of NSAIDs [39]. Adults with knee and/or hip OA consulting a rheumatologist or GP for symptom flare were recruited into the PEGASus study and assigned to a SYSADOA treatment according to the physician's or patient's choice. During up to 24 months' follow-up, SYSADOA switching, continuation or discontinuation was permitted. The SYSADOA treatments included pCGS, GH, CS, avocado soybean unsaponifiables, and diacerein. In the primary analysis, only pCGS achieved a significant reduction in NSAID use, achieving 36% (odds ratio [OR] = 0.64; 95% CI: 0.45–0.92), while for all other treatments virtually no impact on NSAID consumption was measured (GH: OR = 0.98, 95% CI: 0.81–1.19; CS: OR = 0.94, 95% CI: 0.77–1.14; avocado soybean unsaponifiables: OR = 0.98, 95% CI: 0.82–1.17; and diacerein: OR = 1.08, 95% CI: 0.87–1.33) [39].

Pharmacokinetics of glucosamine formulations

The superior efficacy of pCGS may be explained by the patent-protected unique stabilized crystalline formulation of GS [3], among other factors, and the single once-daily dosing regimen (1500 mg) leading to a higher glucosamine concentration in the plasma compared with other preparations [4]. 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 [40], while administration of GH (500 mg tid) leads to steady state levels of only 1.2 μM [41]. In a cross-over study, change from pCGS to GH resulted in a 50% decrease in peak plasma concentration and 75% reduction in total bioavailability [4], which might be explained by the differences in dosing regimen and pharmaceutical formulation. The poor bioavailability obtained with GH may help to understand the negative results obtained with this formulation: for example, in the GAIT study [10], which failed to show a benefit for GH over placebo. Importantly, in OA patients peak glucosamine concentrations at 7.17 μM (range: 3.35–22.7) in the plasma and 4.34 μM (range: 3.22–18.1) in the synovial fluid have been measured after once-daily administration of pCGS (1500 mg) [40,42].

Lack of appropriate stabilization of GS may negatively impact on the active ingredient availability; in addition, the quality of non-prescription grade glucosamine formulations may be sub-optimal [43]. Among 14 dietary supplements and OTC preparations of glucosamine, only one contained the amount of the active ingredient claimed on the package label, while the others contained quantities ranging from 59% to 138% of the labeled dose [43]. Thus, only the prescription pCGS formulation can ensure a reliable delivery of sufficient plasma concentrations of glucosamine in the range shown to be pharmacologically effective.

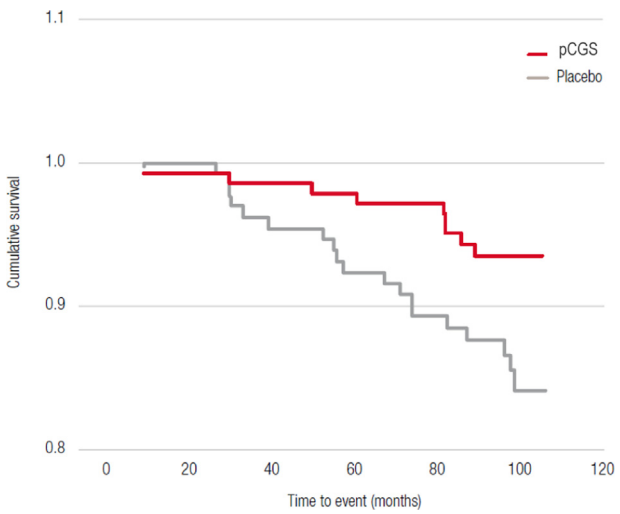

Fig. 2. Effect of prior patented crystalline glucosamine sulfate (pCGS) treatment on cumulative incidence of total joint replacement surgery for up to 5 years following treatment [37]. (Adapted with permission from Bruyere et al. [37].)

Economic impact of glucosamine use

OA is most common in people aged over 50 years, and with the progressive aging of the population in several countries, evaluation of the cost-effectiveness of treatments and impact on healthcare budgets is increasingly important. Economic evaluation allows comparison of different treatment strategies in terms of cost (intervention costs and disease costs) and consequences, e.g., quality-adjusted life years (QALYs). Cost-effectiveness analysis of a 6-month treatment trial has shown pCGS to be a highly cost-effective therapy compared with paracetamol and placebo in the treatment of knee OA, in terms of incremental cost-effectiveness ratio (ICER) [23,44]. Further, a systematic review and economic evaluation has determined the incremental cost per QALY gain for adding GS to current care over a lifetime horizon to be around £21,335 (approx. US$33,346) [45]. Sensitivity analysis determined that the cost-effectiveness of GS therapy was particularly dependent on the magnitude of the quality of life gain, the change in knee TJR probability, and the discount rate.

A real-life follow-up of OA patients has demonstrated that continuous treatment with prescription pCGS results in a reduction in intake of other concomitant medications for OA and in a reduction in healthcare consultations and examinations in the long

Table 2
Mean costs associated with use of OA medication and OA-related healthcare resources per patient per year among OA patients who had received patented crystalline glucosamine sulfate (pCGS) 5 years previously versus placebo [37]

Mean costs, € (US$)[a]	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)
Total cost calculated for OA-related resources[b]	605 (786)	292 (380)[c]

NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; pCGS, patented crystalline glucosamine sulfate. (Adapted from Bruyere et al. [37]).

[a] 1 € (euro) = approx. 1.3 US$ (2007).

[b] Total cost calculation includes costs of secondary healthcare visits (paramedic, specialist), examinations (radiographs, gastroscopies), and medication costs (analgesics, NSAIDs, etc.).

[c] p = 0.024 versus placebo.

term [37]. OA patients who had previously taken part in an RCT attended a follow-up clinic visit (at an average of 5 years after the trial) at which the total average cost of OA-related resources utilized in the year preceding the follow-up visit was calculated to be approximately half among those that had received prescription pCGS versus placebo (€292 versus €605; p = 0.024). The total cost of OA medications taken among the placebo group (including analgesics and NSAIDs) was almost double that of the pCGS group (€204 with placebo versus €108 with pCGS) (Table 2); while the number of specialist, general practitioner (GP) and paramedic visits, and examinations (radiographs, gastroscopies, and non-OA exams) taken in the previous year were consistently higher among the placebo group compared with pCGS patients [37].

Conclusions

There is increasing evidence that different therapeutic effects are obtained with different formulations of glucosamine. Therefore, not all formulations of glucosamine should be afforded the same level of recommendation. High-quality clinical trials have demonstrated the efficacy of prescription pCGS as a SYSADOA, with an effect size on pain greater than that exhibited for paracetamol and in the same range as that obtained for oral NSAIDs. The effect size for other glucosamine preparations has consistently approximated to zero. In this respect, the ESCEO task force advocates prescription pCGS to be recommended in lieu of other glucosamine preparations as a first-line SYSADOA for medium to long-term control of symptoms. Only pCGS is highly bioavailable when administered as a once-daily dose (1500 mg). In addition to a moderate effect on pain, there is evidence that chronic administration can have disease-modifying effects, delaying joint structural changes. Real-life patient cohort follow-up studies have demonstrated that the structure-modifying effects of pCGS appear to translate into clinically relevant benefits in knee OA, i.e., a delay in the need for total joint replacement. Furthermore, real-life, pharmacoeconomic studies have identified a reduction in the need for concomitant pain analgesia and NSAIDs, and the superiority of pCGS versus other glucosamine formulations in this respect.

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All authors meet the ICMJE criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

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