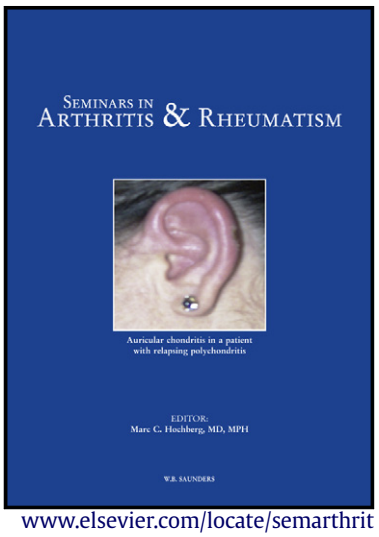

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Efficacy and Safety of Oral Nsaids and Analgesics in the Management of Osteoarthritis: Evidence from Real-Life Setting Trials and Surveys

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Short article

Efficacy and safety of oral NSAIDs and analgesics in the management of osteoarthritis: evidence from real-life setting trials and surveys

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Keywords: analgesics, coxibs, cyclo-oxygenase-2 (COX-2) inhibitors, knee osteoarthritis, oral non-steroidal anti-inflammatory drugs (NSAIDs), tramadol

Abbreviations: AE, adverse event; CV, cardiovascular; GI, gastrointestinal; MI, myocardial infarction; SR, sustained release; UGIC, upper gastrointestinal complications

Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are at the cornerstone of treatment for osteoarthritis (OA). In recent years, the widespread use of oral NSAIDs has been called into question due to the appearance of significant upper gastrointestinal (GI) complications and cardiovascular (CV) adverse events (AEs). However, NSAIDs are non-homogeneous, and there are noticeable differences between them in AE risk for GI and CV events. Nevertheless, if properly prescribed oral NSAIDs can provide an effective and safe treatment for OA in real-life situations. The identification of patients with significant CV and/or GI risk is critical, and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) treatment algorithm provides guidance on appropriate treatments for OA patients with elevated risk. Among non-selective NSAIDs, ibuprofen and naproxen seem preferable to diclofenac, the latter being associated with higher CV risk. Recommendation has been made by some that naproxen may be the preferred agent in patients at high CV risk because of its lower risk of CV events. Low dose celecoxib (200 mg/day) is also associated with a lower risk of CV events compared with other coxibs. In addition, drugs with a demonstrated low GI risk profile may be of benefit, such as coxibs and nabumetone. Among patients who fail to respond adequately to sequential ESCEO algorithm Step 1 and Step 2 treatments, the short-term use of weak opioids, such as tramadol, for severely symptomatic OA patients is recommended. Although studies exploring the efficacy of tramadol in OA are limited, there is good evidence that tramadol works if prescribed properly. The sustained-release (SR) formulation of tramadol is preferred as it avoids the peak plasma concentrations reached with immediate-release tramadol, which is believed to reduce the incidence of AEs. Furthermore, slow upwards titration of tramadol SR is recommended to improve tolerability and minimize treatment discontinuations.

1.0 Introduction

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) treatment algorithm recommends oral non-steroidal anti-inflammatory drugs (NSAIDs) for Step 2 advanced pharmacological management of knee osteoarthritis (OA) if Step 1 treatment shows inadequate efficacy and the patient is still symptomatic, or in patients presenting with moderate-severe pain (1). Oral NSAIDs are universally recommended across the international and national guidelines (see **Table 1**) in patients with persistent symptoms that have not responded adequately to paracetamol with or without topical NSAIDs or, in the ESCEO recommendations, to symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) (1-5). Oral NSAIDs have a moderate effect on pain relief, with an effect size (ES) of 0.29 (95% confidence interval [CI] 0.22 to 0.35) that is greater than that of paracetamol (ES = 0.14; 95% CI 0.05 to 0.22) (6). Use of oral NSAIDs has been associated with greater efficacy in patients with more severe knee and hip OA accompanied by a higher degree of patient preference compared with paracetamol (7). Cyclo-oxygenase-2 (COX-2) selective, partially-selective, or non-selective oral NSAIDs are similarly effective in controlling pain (8). Thus, drug choice is dictated by their safety profile, according to different risk factors, and patients' concomitant diseases and medical conditions (1).

Table 1 Recommendations for the use of oral non-steroidal anti-inflammatory drugs (NSAIDs) for osteoarthritis.

Guideline committee	OA location	Recommendation for oral NSAIDs
European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)	Knee	Recommended when paracetamol or SYSADOAs and/or topical NSAIDs are not adequately effective
European League Against Rheumatism (EULAR)	Knee	Consider in patients unresponsive to paracetamol
American College of Rheumatology (ACR)	Hand, knee, hip	Conditionally recommended for initial therapy; strongly recommended in knee OA patients unresponsive to paracetamol
Osteoarthritis Research Society International (OARSI)	Knee	Appropriate for individuals without relevant co-morbidities; uncertain for those with moderate co-morbidity risk
National Institute for Health and Care Excellence (NICE)	Hand, knee, hip	Use when paracetamol and/or topical NSAIDs are ineffective, or in addition to paracetamol or topical NSAIDs when insufficient pain relief is achieved

Table 1 abbreviations: OA, osteoarthritis; NSAIDs, non-steroidal anti-inflammatory drugs; SYSADOAs, symptomatic slow-acting drugs for osteoarthritis.

Among patients who fail to respond adequately to sequential Step 1 and Step 2 treatments, the ESCEO algorithm recommends the short-term use of weak opioids, such as tramadol, as a last pharmacological treatment before recourse to surgery (1). Similarly, the American College of Rheumatology (ACR) recommends tramadol as an appropriate analgesic in OA pain when non-opioid analgesics, coxibs, and non-selective NSAIDs are poorly tolerated, ineffective, or contraindicated (3). The antidepressant duloxetine is also proposed by the ESCEO at Stage 3 in treatment (1); however, the combination of tramadol and duloxetine is not recommended due to their similar central mechanism of action.

2.0 Examination of the evidence base for oral NSAID safety

The NSAIDs are non-homogeneous as a drug class, and there are vast differences between individual drugs in terms of adverse event (AE) risk for gastrointestinal (GI) and cardiovascular (CV) complications. Thus, the benefit-risk balance of individual NSAIDs is mainly driven by their GI and CV safety profile. The US Food and Drug Administration (FDA) has issued a 'black box' safety warning for the entire oral NSAID drug class highlighting the potential for increased risk of CV events and GI bleeding associated with their use (9).

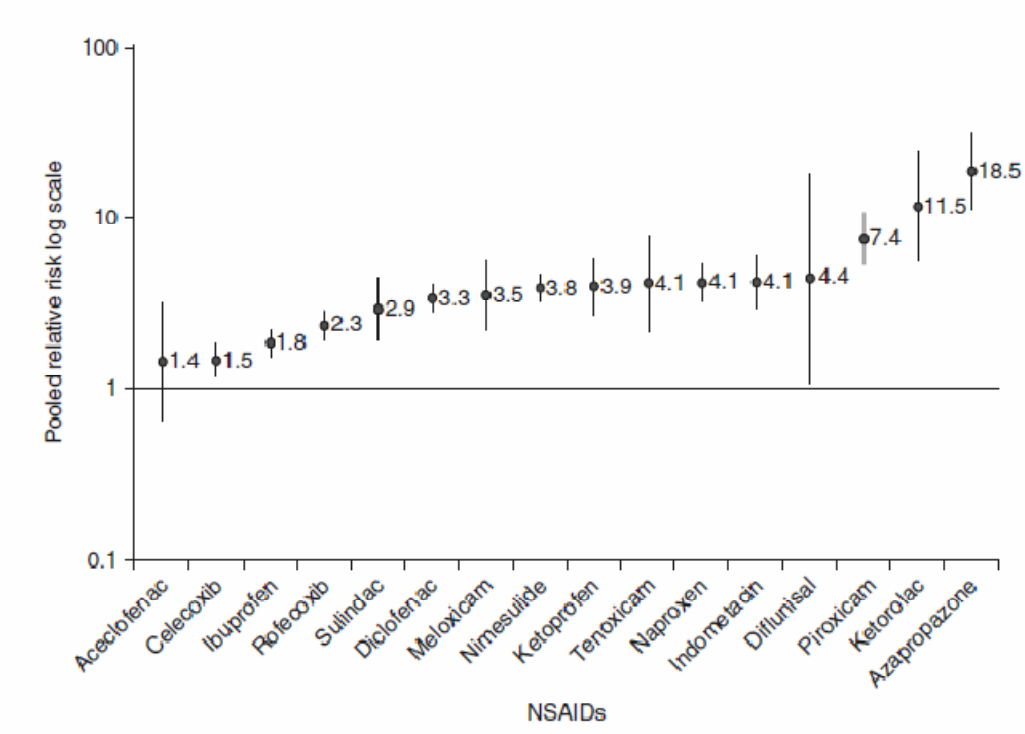
2.1 Upper GI complications

Oral NSAID treatment is associated with a 3- to 5-fold increase in the risk of upper GI complications (UGIC), including peptic ulcer perforation, obstruction and bleeding (10, 11). GI side effects from NSAIDs arise from both topical injury and COX-1 inhibition, which is present even when a parenteral formulation is used, and data indicate a similar safety and tolerability profile with intravenous and oral ibuprofen, for example (12). While COX-2 selective agents are associated with fewer GI ulcer complications, there is still an increased risk of UGIC (13). Systematic review and meta-analyses have identified considerable variability in the risk of UGIC among individual oral NSAIDs as used in clinical practice (13, 14). Piroxicam, ketorolac and azapropazone were associated with the highest relative risk of UGIC, while aceclofenac, celecoxib and ibuprofen were associated with the lowest relative risk, and an intermediate level of risk was found for all other NSAIDs included in the review (**Figure 1**) (13). The high risk of UGIC with indomethacin may be attenuated by use of acemetacin, a pro-drug for indomethacin. Acemetacin is less active on the COX-1 enzyme in

the gastric mucosa, and was found in one study to exhibit similar efficacy in OA with around one-third the incidence of GI AEs found with indomethacin (15). Acemetacin was also demonstrated to have similar efficacy and safety to celecoxib in knee OA treatment over 6 weeks (16). Nabumetone is an NSAID that exhibits equivalent efficacy to many others but with a comparatively good safety profile (17), with 10-fold fewer GI AEs (perforations, ulcers or bleedings) reported across clinical studies compared with other NSAIDs (18, 19).

High daily doses of several NSAIDs are associated with a 2- to 3-fold increase in the relative risk of UGIC compared with low-medium doses, with the exception of celecoxib for which no dose-response relationship was found (13). These findings provide a strong rationale for the use, whenever possible, of low drug dosages for the shorter period of time to minimize GI toxicity.

Figure 1 Pooled relative risks and 95% confidence intervals of upper gastrointestinal complications associated with the use of individual NSAIDs (13). Vertical bars denote 95% CIs.



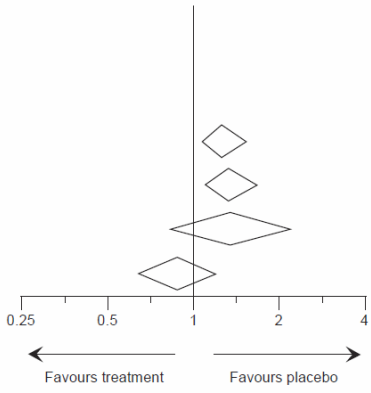
<Figure 1 taken from Castellague 2012 (13); Reproduction granted under Creative Commons Attribution Noncommercial License>

2.2 CV complications

The association of NSAIDs with increased CV risk is a complex issue, but there is today little doubt that all oral NSAIDs, selective and non-selective, have the potential to increase the risk of serious CV events. The coxib and traditional NSAID trialists (CNT) collaboration performed a meta-analysis of 639 RCTs, and found that major vascular events were increased by about a third with a coxib (rate ratio [RR] 1.37; 95% CI 1.14 to 1.66; *p*=0.0009) or diclofenac (150 mg/day) (RR 1.41; 95% CI 1.12 to 1.78; *p*=0.0036) compared with placebo (**Figure 2**) (20). This was largely due to an increase of around three-quarters in the risk of major coronary events. Ibuprofen (2400/day) also significantly increased major coronary events (RR 2.22; 95% CI 1.10 to 4.48; p=0.0253) but not major vascular events (RR 1.44; 95% CI 0.89 to 2.33; p=0.14). In contrast, high dose naproxen (1000 mg/day) was associated with less vascular risk than other NSAIDs (RR 0.93; 95% CI 0.69 to 1.27; *p*=0.66) and no increase in major coronary events (RR 0.84; 95% CI 0.52 to 1.35; *p*=0.48) (20). There was no evidence that any NSAID significantly increased the risk of stroke, although an earlier network meta-analysis had found a higher risk of stroke with ibuprofen (RR 3.36; 95% CI 1.00 to 11.6) (21). While the vascular risks of different coxib regimens appeared similar at the most frequently studied daily doses, there was a trend for lower risk with lower celecoxib doses; although the vascular effects of the most widely used coxib regimen, celecoxib 200 mg/day, were statistically uncertain (20). Vascular risk is likely related to the degree of COX-2 inhibition, which increases with dose, suggesting a dose-dependent effect.

Figure 2 Effects of coxib and traditional NSAID treatment on risk of major vascular events (20).

Treatment	RR coxib vs. other treatment (95% CI)	Adjusted RR vs. placebo (95% CI)	p
Coxib	–	1.37 (1.14-1.66)	0.0009
Diclofenac	0.97 (0.84-1.12)	1.41 (1.12-1.78)	0.0036
Ibuprofen	0.92 (0.58-1.46)	1.44 (0.89-2.33)	0.14
Naproxen	1.49 (1.16-1.92)	0.93 (0.69-1.27)	0.66



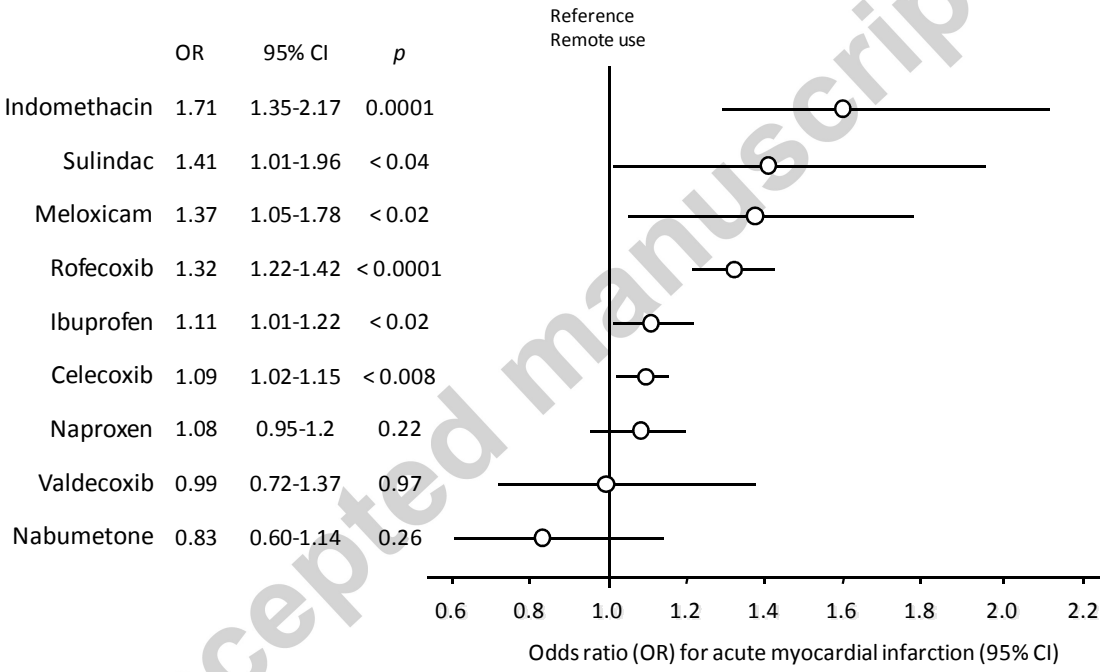
Major vascular events includes: non-fatal myocardial infarction (MI), coronary death, MI or coronary heart disease, non-fatal stroke, stroke death, any stroke, other vascular death.

CI, confidence interval; RR, rate ratio.

<Figure 2 Adapted from Bhala 2013 (20)>

The risk of acute myocardial infarction (MI) with individual coxibs and non-selective oral NSAIDs was also previously assessed in a large nested case-control study that included over 2,356,885 person-years of follow-up and 15,343 cases of acute MI (22). Indomethacin, sulindac, and meloxicam were associated with the highest increased risk of acute MI, while nabumetone was associated with the lowest risk of acute MI (**Figure 3**). Among the coxibs, rofecoxib was associated with the highest risk, while celecoxib (all dosages) and low dose valdecoxib (20 mg/day) were associated with the lowest risk of acute MI (22).

Figure 3 Risk for acute myocardial infarction with non-selective NSAIDs and COX-2 inhibitors (22).

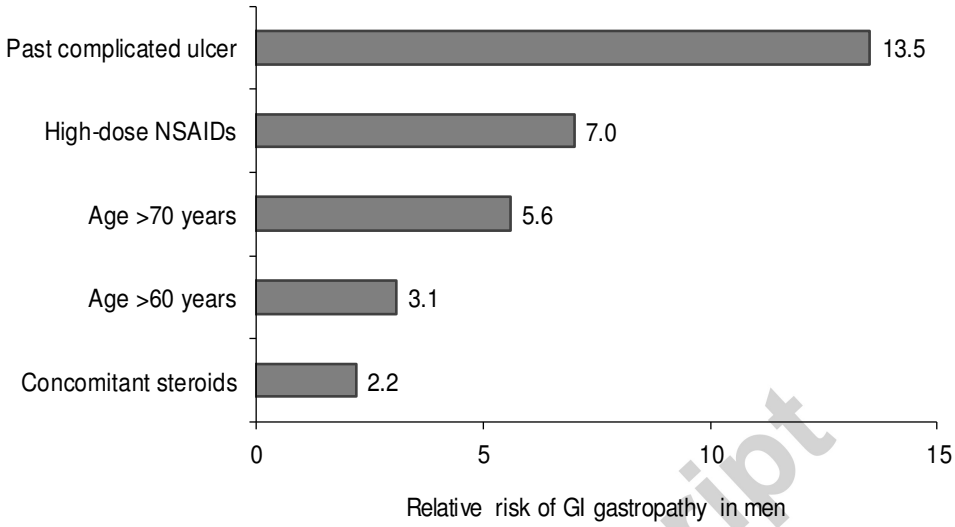


<Figure 3 adapted from Singh EULAR 2005 (22)>

3.0 Guidance on use of NSAIDs in real-life OA patients

The choice of NSAID to use in clinical practice depends on individual patient characteristics and medical history. Several patient factors have been identified to increase the risk of UGIC, including advanced age, a history of GI ulcer, and concomitant treatment with corticosteroids, aspirin or anticoagulants (**Figure 4**) (23, 24). The ESCEO recommends that patients are assessed for risk factors and the risk:benefit ratio of treatment is determined before making treatment decisions. Patient preference is an important consideration, for example, of dosing regimen whether once-daily or more frequent dosing is desirable.

Figure 4 Clinical risk factors for gastrointestinal gastropathy (24).



<Figure 4 Adapted from Hunt 2002 (24)>

GI complications associated with oral NSAID use are the most common serious adverse drug reactions in the US. A large majority of NSAID-associated GI adverse events (AEs) are asymptomatic until a complication occurs, i.e. they are not preceded by mild side effects such as abdominal pain and vomiting (25). The use of concomitant gastroprotective agents such as proton pump inhibitors (PPIs) are the most commonly recommended treatments to reduce the risk of GI complications with non-selective NSAIDs. Moreover, concomitant use of high dose of famotidine or misoprostol can also reduce the occurrence of gastric ulcer complications by 50–60% (26). Among patients with a prior history of ulcer bleeding, treatment with diclofenac plus omeprazole was shown to be as safe as treatment with celecoxib, with respect to the prevention of recurrent bleeding (27).

While coxibs are associated with a lower risk of UGIC compared with non-selective NSAIDs, there is still a significant increase in risk compared with placebo (20). The ESCEO algorithm recommends that in patients with low (normal) GI risk, it should be considered to prescribe either a non-selective NSAID with or without a PPI or a COX-2 selective NSAID, based on the judgment of the clinicians. 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 (28) (**Table 2**).

Table 2 ESCEO recommendations for Step 2 advanced pharmacological management of persistent symptoms in patients with osteoarthritis using oral NSAIDs (1).

Intermittent or continuous (longer cycles) oral NSAIDs			
Normal GI risk	**Increased GI risk***	**Increased CV risk**	**Increased renal risk**
• Non-selective NSAID with PPI • COX-2 selective NSAID (consider PPI)	• COX-2 selective NSAID with PPI • Avoid non-selective NSAIDs	• Prefer naproxen • Avoid high-dose diclofenac and ibuprofen (if on low-dose aspirin) • Caution with other non-selective NSAIDs • Avoid COX-2 selective NSAIDs	• Avoid NSAIDs†

*Including use of low-dose aspirin; †with glomerular filtration rate <30 cc/min, caution in other cases; COX-2, cyclooxygenase-2; CV, cardiovascular; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

<Table 2 adapted from Bruyere 2014 (1)>

Regarding CV risk associated with oral NSAID use, early evidence suggested that the relative risk of CV events increased with increased baseline CV risk (29); although a recent and comprehensive meta-analysis found that the proportional increase in risk was similar irrespective of baseline risk (20). Thus, these drugs should be avoided in high CV risk patients and probably other non-selective NSAIDs as well. Ibuprofen should not be used with concomitant low-dose aspirin due to clinically relevant pharmacological interaction (30). Naproxen is the exception, and may be the preferred agent if an NSAID is required in patients at high CV risk, because of its lower risk of CV events (20, 31). The lower risk of CV thrombovascular events associated with naproxen may be due to its sustained suppression of platelet aggregation (20). In a 2012 report, the European Medicines Agency (EMA) stated that naproxen may be associated with a lower risk of arterial thrombotic events than COX-2 inhibitors and other NSAIDs (32). In addition, following a review of CV safety, the EMA issued a warning for oral diclofenac treatment not to be prescribed to patients with ischemic heart disease, peripheral arterial disease, cerebrovascular disease, or established congestive heart failure, which was subsequently endorsed by the European Commission (33). The ESCEO and ACR recommend that oral NSAID use is avoided in patients with increased renal risk, such as chronic kidney disease with estimated glomerular filtration rate below 30 cc/min (1, 3).

Due to the risk of GI and CV events, the product information for all NSAIDs recommends that these medicines be used at the lowest effective dose for the shortest period of time necessary to control symptoms (32). The ESCEO algorithm recommends that oral NSAIDs may be used intermittently or continuously in longer cycles rather than in chronic use, because of safety concerns and a lack of long-term trials (1). A recent short-term trial of low-dose celecoxib (200 mg/day) found that continuous treatment with celecoxib over 22 weeks was significantly more effective than intermittent use in preventing OA flares of the hip and knee without an increase in overall AEs including GI disorders and hypertension (34). However, the select population included in the trial has low risk CV and GI risks and, therefore, is not representative of the general OA patient population.

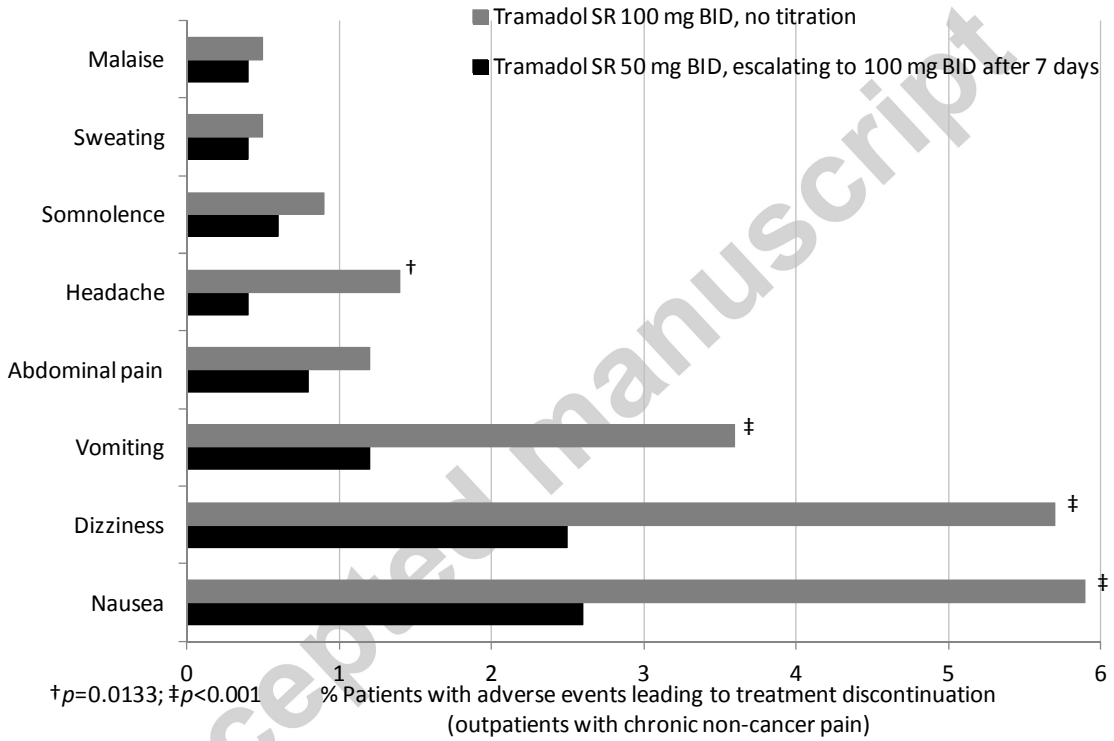
In the event of insufficient control of symptoms with an NSAID, the combination of NSAIDs is not recommended by the ESCEO task force, as there is no evidence of additional benefit, and an increased risk of AEs, with additional cost of treatment. While switching NSAIDs may provide some benefit, the ESCEO task force does not recommend multiple successive rounds of NSAIDs before considering other treatment options. If the patient is still symptomatic despite use of NSAIDs, the ESCEO algorithm recommends intra-articular treatment, or recourse to short-term weak opioids, e.g. tramadol (1).

4.0 Pharmacological treatment with weak opioids

Among OA patients who fail to respond adequately to pharmacological treatments, including oral NSAIDs, the ESCEO algorithm recommends the short-term use of weak opioids, such as tramadol, as one of the last pharmacological treatments before recourse to surgery (1). Tramadol is a synthetic, centrally-acting analgesic with opioid agonist properties that acts on the neurotransmission of norepinephrine and serotonin. In addition, tramadol modifies the transmission of pain impulses by inhibition of monoamine reuptake. Tramadol rarely causes the AEs of respiratory depression and physical dependence commonly associated with conventional opioid drugs, since its analgesic effects are through both weak opioid and non-opioid mechanisms (35). Tramadol is not attributed with the GI and CV AEs associated with NSAIDs (36). However, the use of tramadol may be impeded by non-serious AEs, predominantly nausea and headache, resulting in treatment withdrawal and sub-optimal pain management (37, 38). Sustained release (SR) formulations of tramadol may improve tramadol tolerability and reduce the incidence of AEs (39). SR formulations are associated with prolonged effective plasma levels of tramadol, while preventing the high plasma peaks associated with AEs seen with the immediate-release formulations (39, 40). In addition, multiple-unit SR capsule formulation produces a smoother and extended tramadol plasma

concentration profile compared with single-unit SR tablets due to a more gradual release of tramadol (39). Further, the slow upward titration of SR tramadol is recommended to minimize AEs and premature treatment discontinuations (41). The dose titration of multiple-unit SR tramadol leads to a reduced incidence of AEs and reduced frequency of treatment discontinuations (**Figure 5**) (41).

Figure 5 Effect of dose titration of multiple-unit SR tramadol (50 to 100 mg bid, over 7 days) on incidence of AEs leading to treatment discontinuations.



<Figure 5 Adapted from Tagarro 2005 (41)>

A Cochrane review of RCTs showed that the efficacy of tramadol in relieving pain and improving function in knee OA is small but significant, although AEs are significantly increased over placebo and may lead to treatment withdrawal (36). Treating OA patients with short-term tramadol may decrease pain, reduce stiffness and improve function, and overall well-being (36). In a placebo-controlled study of tramadol in patients with OA, patients did significantly better with tramadol than with placebo (42).

5.0 Conclusions

NSAIDs are non-homogeneous, and there are vast differences in AE risk for GI and CV events. Nonetheless, if properly prescribed oral NSAIDs can provide an effective and safe treatment for OA. The identification of patients at risk of significant CV and/or GI side effects is crucial, and the ESCEO algorithm provides guidance on appropriate treatments for OA patients with elevated risk. Low dose celecoxib (100–200 mg/day) is associated with a lower risk of CV events compared with other coxibs and diclofenac. Among non-selective NSAIDs, ibuprofen and naproxen are preferable to diclofenac. In addition, other drugs with a demonstrated low risk AE profile may be of benefit such as nabumetone and acemetacin, which shows similar efficacy and safety to celecoxib. Intermittent cycles of treatment are usually preferable than continuous administration, to minimize the risk of AEs. The combination of NSAIDs is discouraged as this provides no additional benefit, with an increased risk of AEs and additional cost. Multiple successive rounds of NSAIDs should also be avoided in patients with persistent symptoms before considering subsequent steps in the ESCEO recommended treatment algorithm.

The short-term use of soft weak opioids, such as tramadol, may be considered for severely symptomatic OA patients. Although studies of tramadol are limited in OA, there is good evidence that tramadol works if prescribed properly. The SR formulation of tramadol is preferred as it avoids the peak plasma concentrations, and consequently reduces the incidence of side effects. Furthermore, slow upwards titration of SR tramadol is recommended to improve tolerability and minimize treatment discontinuations due to AEs.

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All authors meet the ICMJE criteria for authorship for this manuscript, 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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