دانشگاه علوم پزشکی و خدمات
بهداشتی و درمانی گلستان

مرکز تحقیقات روماتولوژی

Use of NSAIDs in RHEUMATIC DISEASE

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Rheum Diseases You Will Encounter

مرکز تحقیقات روماتولوژی

- • Osteoarthritis
- • Rheumatoid Arthritis
- • Seronegative spondyloarthropathy
- • Crystal-induced arthritis
- • Systemic lupus erythematosus
- • Vasculitis
- – Scleroderma, Inflammatory Myopathy
- …..

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Non
Steroidal
Anti
Inflammatory
Drug

	Maximum Recommended Daily Dose	Usual Dosage (Oral)
Diclofenac	150 mg	75 mg 2 times a day or 50 mg 3 times a day 100 mg once/day sustained-release
Ibuprofen	3200 mg	400–800 mg 4 times a day
Indomethacin	200 mg	25 mg 3 to 4 times a day 75 mg 2 times a day sustained-release
Meloxicam	15 mg	7.5 mg once/day
Naproxen	1500 mg	250–500 mg 2 times a day
Celecoxib	400 mg	200 mg once/day or 2 times a day

Pain Ther (2021) 10:783–808
https://doi.org/10.1007/s40122-021-00260-1

REVIEW

Management of Osteoarthritis: Expert Opinion on NSAIDs

Alberto Magni · Piergiuseppe Agostoni · Cesare Bonezzi · Giuseppe Massazza · Paolo Menè · Vincenzo Savarino · Diego Fornasari

- **Osteoarthritis (OA) is the most frequent form of arthritis worldwide and a leading cause of disability among older adults .**

- **its prevalence is 24.9% in women and 16% in men and is highest in persons aged > 85 years (63.0% in women and 50.9% in men)**

- **After hypertension, it is the second most common chronic disease managed by general practitioners (GPs)**

Practical Indications

1. During the visit, pain must be thoroughly evaluated, considering:
    1. pain origin and duration
    2. component (inflammatory or degenerative)
    3. NSAID activity (peripheral or central)
2. Consider possible factors that increase the risk of CV, GI and renal AEs.
3. Calculate the CV risk.

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Are All NSAIDs Equal?

- there are several differences among NSAIDs that impact on their efficacy and safety .These include:
- *COX isoform selectivity and potency*
- *Plasma half-life*.
- *Interference with ASA*
- *Penetration into the synovial liquid*
- *Passage through the blood–brain barrier*

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Factors Influencing the Individual Response to NSAIDs

- Genetic variations
- The microbiota
- The possibility of phenotyping OA
- Gender

By When Should We Expect the Response to NSAID treatment?

- Usually, the maximum peak plasma concentration is reached within 2–3 h of administration, but the efficacy also depends on other factors.

- The analgesic effect occurs within about 1 week and the full anti-inflammatory effect is often achieved in 3 weeks.

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What is the Adequate Duration of NSAID Therapy?

- NSAIDs should be used for the shortest duration possible and at the lowest dose that guarantees both inflammation reduction and physical function improvement

- If at the end of the 3-week period no result has occurred, a switch to another agent should be attempted

Monotherapy or Combination Therapy?

- It is possible to combine NSAIDs with central analgesics, such as paracetamol and opioids
- the combination of NSAIDs with steroids should be avoided

- Coxibs, diclofenac and ibuprofen displayed a similar relative risk for CV events (range 1.37–2.49), whereas naproxen did not seem to increase it

- coxibs, diclofenac and ibuprofen also displayed a comparable annual absolute risk for major vascular events

- subsequent network meta-analysis found no difference in the risk of major CV events with diclofenac, ibuprofen, naproxen, celecoxib and etoricoxib for the treatment of pain in patients with OA or RA

- A recent meta-analysis of individual patient data in real-world settings has shown that all traditional NSAIDs are associated with an increased risk of AMI, similar to that reported with celecoxib therapy. Using a high daily dose (celecoxib > 200 mg, diclofenac > 100 mg, ibuprofen > 1200 mg, naproxen > 750 mg) for 8–30 days was associated with the greatest risk, which did not increase further beyond the first 30 days.

- Based on these findings, prescribers should consider weighing the risks and benefits of NSAIDs before selecting the treatment, particularly for higher doses.

- Finally, it must be pointed out that the concomitant administration of certain NSAIDs weakens the protective CV effects of ASA

- Co-administration of ibuprofen in patients with documented CVD on low-dose ASA therapy significantly increased the risk of all-cause and CV mortality (hazard ratio [HR] 1.93, 95% confidence interval [CI] 1.30–2.87; HR 1.73, 95% CI 1.05–2.84, respectively) compared to ASA alone

- No difference was observed when diclofenac or other NSAIDs were used with ASA versus ASA alone

Practical Indications

1. Avoid the use of paracetamol in case of inflammatory pain.
2. NSAIDs should be used for the shortest duration and at the lowest dose that guarantees the effect on inflammation and improvement in physical function.
3. Define therapy duration based on the patient profile and avoid the on-demand use of NSAIDs: in the case of inflammatory pain, therapy must be administered for at least 10 days to achieve analgesia and for 3 weeks to achieve the full anti-inflammatory effect.
4. It is possible to combine NSAIDs with central analgesics such as paracetamol and opioids.
5. Avoid the combination of NSAIDs with steroids.
6. Consider formulations relying on one or few administrations to improve adherence.

Table 1 The main factors that increase the risk of cardiovascular, gastrointestinal and renal complications to be considered before starting a therapy with non-steroidal anti-inflammatory drugs in patients with osteoarthritis

Main risk factors for NSAID-associated AEs		
CV	**GI**	**Renal**
Age	Past complicated ulcer	Older age
Gender	Multiple NSAIDs, including ASA	Risk of dehydration
Smoking	Concomitant anti-coagulants, ticlopidine and clopidogrel	Frequent need for contrast media radiologic diagnostic procedures
Comorbidities (e.g. hypertension, diabetes, obesity, heart failure, CVD)	Past-uncomplicated ulcer	Comorbidities
		Atherosclerosis
Concomitant therapies (e.g. diuretics, antibiotics, nephrotoxic drugs, low-dose ASA)	Age > 65 years	CVD (e.g. chronic heart failure)
		Liver cirrhosis
Hospitalization	Steroids	Chronic glomerular disease
Lifestyle		Nephrotic syndrome
Use of OTC NSAIDs		Diabetes
Hyperlipidemia		Hypertension
Coronaropathy		NSAID-related allergy
Cerebrovascular disease		Concomitant therapies
Peripheral Vasculopathy		ACE-inhibitors
COPD		ANG II-receptor antagonists
Concomitant antiaggregant therapy		High-dose diuretics

Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis

WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous systematic reviews have reported on the effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids to treat osteoarthritis pain

These reviews clustered drug doses or drug classes in their analyses

WHAT THIS STUDY ADDS

Etoricoxib 60 mg/day and diclofenac 150 mg/day seem to be the most effective oral NSAIDs for knee and hip osteoarthritis pain and physical function, but might not be appropriate in the presence of comorbidities or for long term use

Topical diclofenac 70-81 mg/day could be effective and generally safer because of reduced systemic exposure and lower dose, and should be considered as first line pharmacological treatment for knee osteoarthritis

The clinical benefit of opioid treatment, regardless of preparation or dose, does not outweigh the harm it might cause in patients with osteoarthritis

Table 3. Strategies for reducing cardiovascular risk

If using aspirin, take aspirin dose ≥2 hours prior to NSAID dose[a]
Do not use NSAIDs within 3 to 6 months of an acute cardiovascular event or procedure
Carefully monitor and control blood pressure
Use low-dose, short half-life NSAIDs and avoid extended release formulations

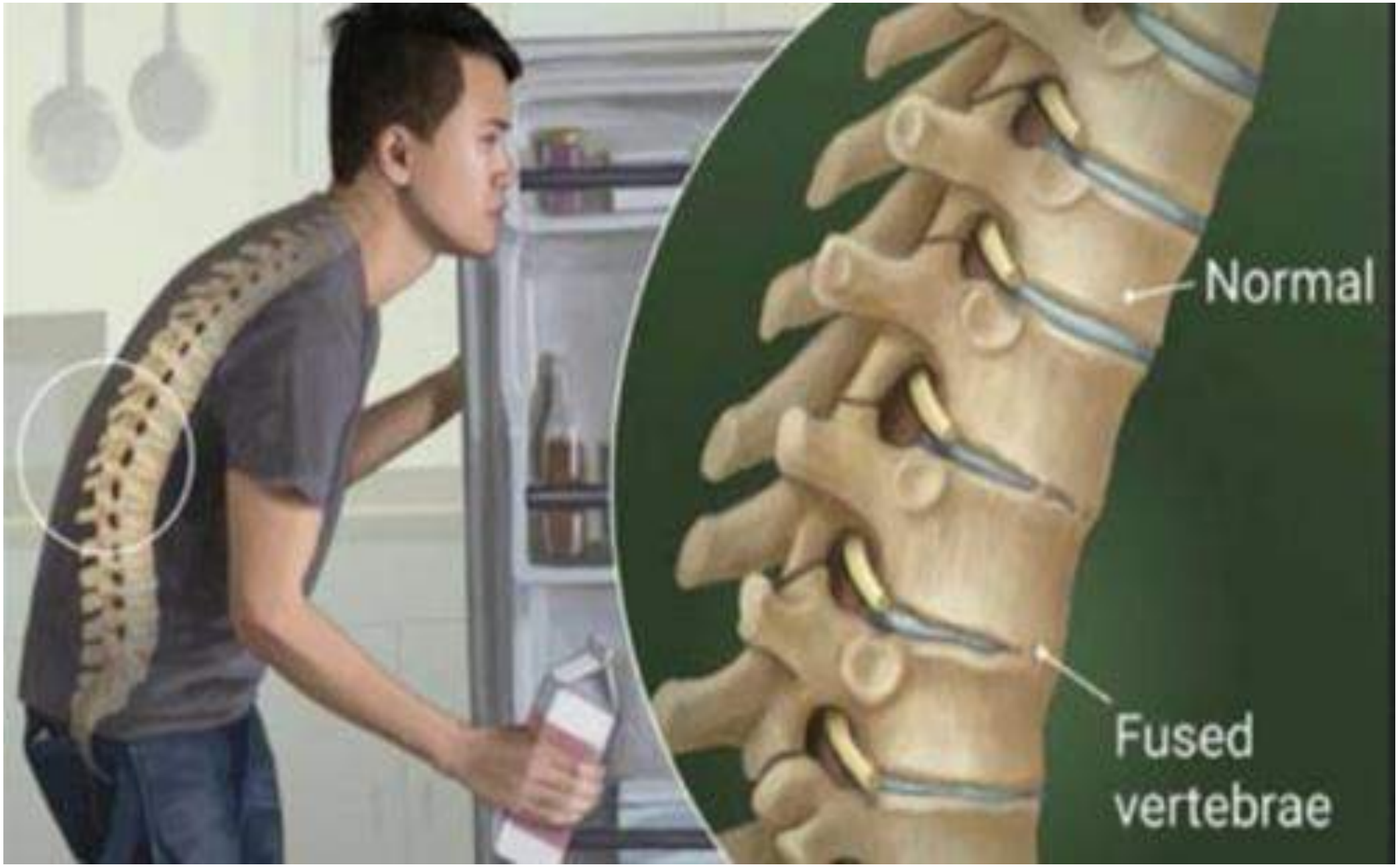
Reprinted with permission from [1]. [a]Especially ibuprofen and does not include celecoxib.

Non-steroidal anti-inflammatory drug use and outcomes of COVID-19 in the ISARIC Clinical Characterisation Protocol UK cohort: a matched, prospective cohort study

Thomas M Drake, Cameron J Fairfield, Riinu Pius, Stephen R Knight, Lisa Norman, Michelle Girvan, Hayley E Hardwick, Annemarie B Docherty, Ryan S Thwaites, Peter J M Openshaw, J Kenneth Baillie, Ewen M Harrison*, Malcolm G Semple*, for the ISARIC4C Investigators†

Results Between Jan 17 and Aug 10, 2020, we enrolled 78 674 patients across 255 health-care facilities in England, Scotland, and Wales. 72 179 patients had death outcomes available for matching; 40 406 (56·2%) of 71 915 were men, 31 509 (43·8%) were women. In this cohort, 4211 (5·8%) patients were recorded as taking systemic NSAIDs before admission to hospital. Following propensity score matching, balanced groups of NSAIDs users and NSAIDs non-users were obtained (4205 patients in each group). At hospital admission, we observed no significant differences in severity between exposure groups. After adjusting for explanatory variables, NSAID use was not associated with worse in-hospital mortality (matched OR 0·95, 95% CI 0·84–1·07; p=0·35), critical care admission (1·01, 0·87–1·17; p=0·89), requirement for invasive ventilation (0·96, 0·80–1·17; p=0·69), requirement for non-invasive ventilation (1·12, 0·96–1·32; p=0·14), requirement for oxygen (1·00, 0·89–1·12; p=0·97), or occurrence of acute kidney injury (1·08, 0·92–1·26; p=0·33).

Interpretation NSAID use is not associated with higher mortality or increased severity of COVID-19. Policy makers should consider reviewing issued advice around NSAID prescribing and COVID-19 severity.


Normal
Fused
vertebrae

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ARD

Comparative efficacy of non-steroidal anti-inflammatory drugs in ankylosing spondylitis: a Bayesian network meta-analysis of clinical trials

Runsheng Wang, Abhijit Dasgupta and Michael M Ward

Ann Rheum Dis published online August 6, 2015

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- **Etoricoxib was more effective in reducing pain in AS than some other NSAIDs, but there was otherwise insufficient evidence to conclude that any particular NSAID was more effective in the treatment of AS.**

Cochrane Library

Cochrane Database of Systematic Reviews

Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) (Review)

- **High to moderate quality evidence indicates that both traditional and COX-2 NSAIDs are efficacious for treating axSpA, and moderate to low quality evidence indicates harms may not differ from placebo in the short term. Various NSAIDs are equally effective. Continuous NSAID use may reduce radiographic spinal progression, but this requires confirmation.**

Received: 18 October 2017 | First decision: 6 November 2017 | Accepted: 18 February 2018
DOI: 10.1111/apt.14606

WILEY AP&T Alimentary Pharmacology & Therapeutics

Systematic review with meta-analysis: association between acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) and risk of Crohn's disease and ulcerative colitis exacerbation

- **Contrary to generally accepted belief, we did not find a consistent association between NSAIDs use and risk of CD and UC exacerbation. There was also no consistent evidence for association with acetaminophen although further studies are needed.**

Current Rheumatology Reports (2021) 23: 4
https://doi.org/10.1007/s11926-020-00967-8

CRYSTAL ARTHRITIS (M PILLINGER & M TOPROVER, SECTION EDITORS)

Something Old, Something New: the ACR Gout Treatment Guideline and Its Evolution from 2012 to 2020

The 2020 guideline strongly recommends colchicine, NSAIDs, or glucocorticoids (oral, intra-articular, or intramuscular) over IL-1 inhibitors or adrenocorticotropic hormone (ACTH) for initial management gout flares

Differences in the Approach to Inflammatory Prophylaxis:

The 2012 guidelines offered a very specific prescription for continuing anti-inflammatory prophylaxis, with multiple contingencies resulting in a minimum treatment period of 6 months. In contrast, in the 2020 guideline, it is strongly recommended that prophylaxis should continue for a minimum of 3 to 6 months with continual evaluations. If the patient continues to experience gout flares, it is recommended to continue the prophylaxis.

Lupus (2001) 10, 135–139

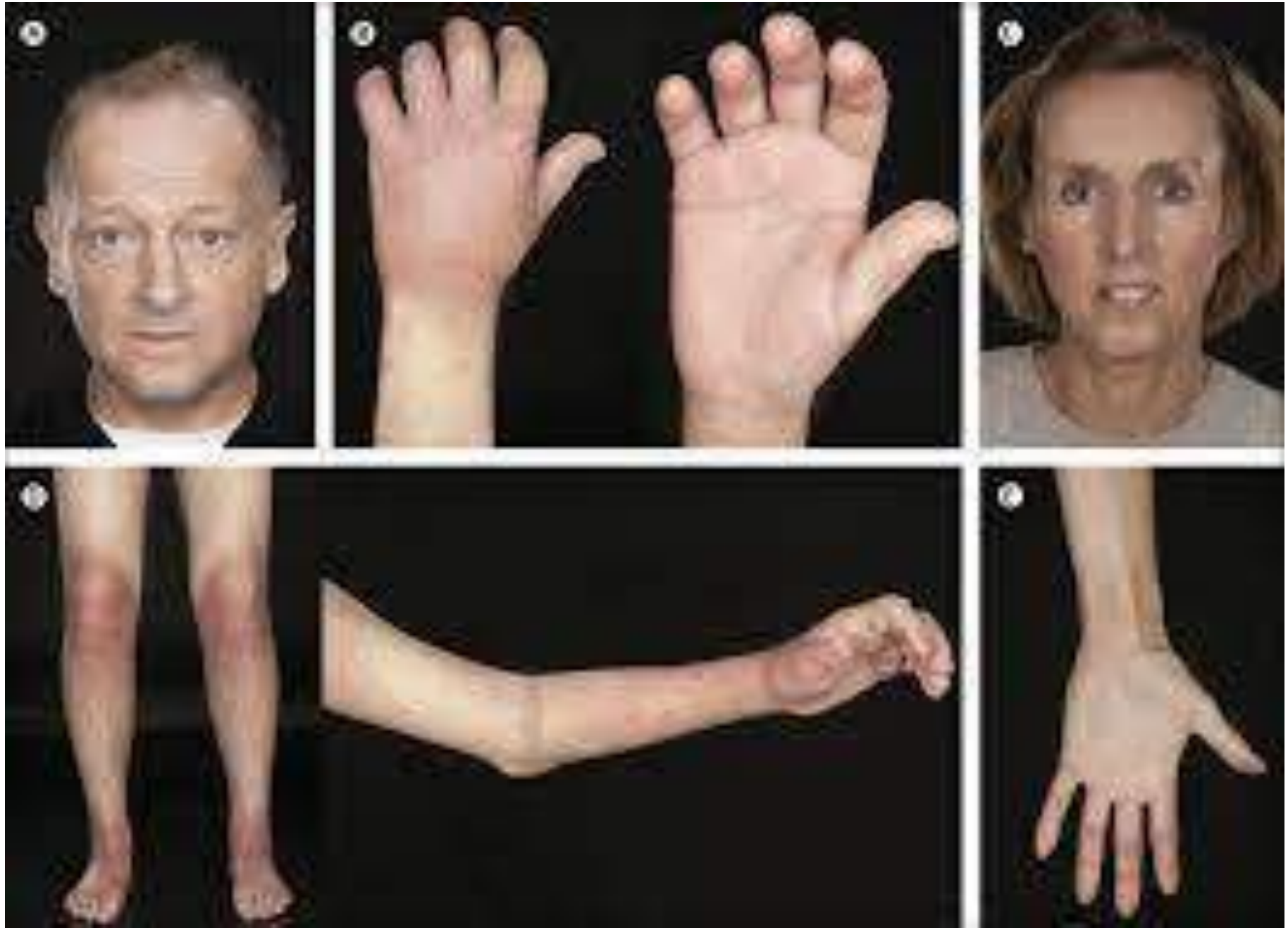
0961–2033
www.arnoldpublishers.com/journals

REVIEW

Nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus

Table 1 Practice points for the prescription of NSAID in SLE

Side effects	*Key points*	*Recommendations*
Gastrointestinal side effects	GI involvement is frequent in SLE, complications may be masked by concomitant corticosteroids.	Consider prescription of Cox-2 selective inhibitors
Renal side effects	Decrease in kidney function. Water and electrolyte disturbances. Beneficial effect of NSAID in nephrotic syndrome	Monitor fluid state, body weight, blood pressure, creatinine, sodium and potassium
Cutaneous side effects	Allergic and skin reactions are increased in SLE patients.	Caution with NSAID prone to induce phototoxic reactions in SSA/B positive patients
Hepatic side effects	Hepatotoxicity is a frequent side effect of high dose aspirin, sulindac and diclofenac.	Monitoring of transaminases at regular intervals during the first 6 months of NSAID therapy
CNS side effects	A variety of CNS reactions to NSAID are mild. Aseptic meningitis, though rare, is most frequently seen with ibuprofen	Awareness of the possibility of NSAID induced CNS symptoms. Discontinuation of NSAID at unexplained CNS symptoms.
Effects on reproduction	Inhibition of ovulation by NSAID may occur. Risk of fetal renal and cardiac side effects at exposure to NSAID in late gestation	Stop NSAID if unexplained infertility. Discontinue NSAID at gestational week 32.

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Gordon et al. BMC Nephrology (2019) 20:279
https://doi.org/10.1186/s12882-019-1467-y

BMC Nephrology

RESEARCH ARTICLE Open Access

Systemic sclerosis medications and risk of scleroderma renal crisis

- **While NSAID use was common in SSc there was no association with future development of SRC.**

Thank you