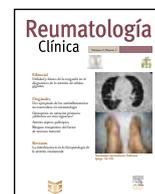


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Original Article

Appropriate Use of Non-steroidal Anti-inflammatory Drugs in Rheumatology: Guidelines From the Spanish Society of Rheumatology and the Mexican College of Rheumatology

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ABSTRACT

Objective: To develop guidelines for the appropriate use of NSAIDs in rheumatology.

Methods: We used a methodology modified from the one developed by RAND/UCLA. Two groups of panellists were selected, one by the CMR and another by the SER. Recommendations were proposed from nominal groups and the agreement to them was tested among rheumatologists from both societies by a 2-round Delphi survey. The analysis of the second Delphi round supported the generation of the final set of recommendations and the assignment of a level of agreement to each of them. Systematic reviews of 5 recommendations in which the agreement was low or was divided were also carried out.

Results: Here we present recommendations for the safe use of NSAIDs in rheumatic diseases, based on the best available evidence, expert opinion, the agreement among rheumatologists, and literature review. The trend is to reduce the frequency, duration, and dose of NSAIDs in favour of non-pharmacological measures, analgesic drugs, or disease modifying drugs. In addition, the recommendations help to identify profiles for increased toxicity, with an emphasis on gastrointestinal and cardiovascular risks. The recommendations deal with the course of action and monitoring in different risk groups and in patients using antiplatelet or anticoagulant drugs. The overall level of agreement is high.

Conclusions: The NSAIDs are safe and effective drugs for the treatment of rheumatic diseases. However, it is necessary to individualize its use according to their risk profile.

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Uso apropiado de los antiinflamatorios no esteroideos en reumatología: documento de consenso de la Sociedad Española de Reumatología y el Colegio Mexicano de Reumatología

RESUMEN

Palabras clave:
Antiinflamatorios
Recomendaciones
Técnica Delphi
Revisión

Objetivos: Elaborar recomendaciones para el uso apropiado de AINE en reumatología.

Métodos: Se utilizó una metodología modificada de RAND/UCLA. Se seleccionaron dos grupos de panelistas, uno por el CMR y otro por la SER. A partir de grupos nominales, se obtuvieron propuestas de recomendaciones, que fueron sometidas a la prueba de acuerdo entre los reumatólogos de ambas sociedades mediante encuesta Delphi a dos rondas. Del análisis de la segunda ronda Delphi, se extrajeron las recomendaciones finales y posteriormente se revisó el nivel de evidencia y el grado de acuerdo de la recomendación según el Centro de Medicina Basada en la Evidencia de Oxford. Finalmente, se efectuó revisión sistemática de cinco recomendaciones sin acuerdo.

Resultados: Se presentan recomendaciones sobre el uso seguro de los AINE en las enfermedades reumáticas, con base en la mejor evidencia disponible, la opinión de expertos, el acuerdo entre reumatólogos y la revisión de la literatura. La tendencia es disminuir la frecuencia, la duración y la dosis de AINE en favor de medidas no farmacológicas, analgésicos o fármacos modificadores de los síntomas o del curso de la enfermedad. Además, es obligado identificar perfiles de mayor riesgo de toxicidad, en especial gastrointestinal y cardiovascular. Se recomiendan pautas de actuación y monitorización en los diferentes grupos de riesgo y en pacientes con empleo de antiagregantes plaquetarios, anticoagulación o con terapias concomitantes. El porcentaje de acuerdo es elevado en la mayoría de los casos.

Conclusiones: Los AINE son medicamentos seguros y eficaces en el tratamiento de las afecciones reumáticas. No obstante, dado su perfil de riesgo, es necesario individualizar su uso.

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Introduction

Non-steroidal anti-inflammatory drugs (NSAID) are among the most consumed drugs worldwide.¹ According to data from EPISER, a national database on rheumatic disease, between 24% and 64% of the patients with rheumatic disease consume NSAID.² This data is confirmed by the Pharmacotherapeutic Reports of the Spanish National Health System, in which NSAID occupy the first place in drug sales, with more than 42 million units sold, representing approximately 370 Euros in 2003 only.³

The main indication for the use of NSAID in rheumatology is for the treatment of pain; however, their efficacy goes beyond that because they are useful for alleviating symptoms of inflammation and lead to an important improvement in the quality of life and the physical function of patients with diverse acute and chronic rheumatic diseases. In addition, patients usually prefer NSAID to paracetamol or other analgesics for the treatment of their rheumatic illnesses.⁴

In the past years, with the introduction of cyclo-oxygenase 2 specific inhibitors (known as coxibs), and substantial changes in the treatment of rheumatic disease, important advances in the knowledge of the efficacy of NSAID has been gained, but also and in particular regarding their safety.⁵ Therefore, their cardiovascular⁶ and gastrointestinal safety profile as well as other new aspects, for example costs, have been explored.⁷ The increase in information, however, is not always accompanied by an increase in confidence in the handling of these drugs, probably because the amount of information reaches unmanageable quotas and is contradictory in appearance, depending on the point of view of who presents it.⁵⁻¹³

For these reasons, the Spanish Society of Rheumatology (SER) and the Mexican College of Rheumatology (CMR) decided to elaborate a document, based on the current medical evidence and in expert opinion, which reviewed both known and infrequent, on the use of NSAID in daily clinical practice, and the result is the present consensus on the adequate use of NSAID in rheumatology.

Methods

The methodology used for the development of this consensus is based on a modification of the RAND/UCLA methodology.¹⁴ Nominal

groups were formed, Delphi surveys and systematic reviews of facts or conflicting recommendations were carried out.

Establishment of the SER and CMR Panel Groups

The Research Unit of the Spanish Foundation of Rheumatology (UIFER), as well as SER and CMR, selected a group of panelists according to the following criteria: *a*) had published articles on the use, pharmacology, or effects of NSAID; and *b*) that the articles published appeared on MEDLINE, *Reumatología Clínica*, or the older official journals (*Revista Española de Reumatología* or *Revista del Colegio Mexicano de Reumatología*). Then 2 independent meetings were carried out with each nominal group (CMR and SER), as well as several successive joint meetings.

Meeting of the Nominal Groups and Delphi Surveys

In the meetings, moderated by members of the UIFER with experience in group methodology, the reach and terminology to be employed were defined, as well as aspect classification and themes to be developed, the definition of the risk of toxicity, and recommendation proposals were made. With the definitions generated and consented, the Delphi surveys were created in 2 rounds, as is shown in Figure 1.

The first round of the Delphi survey was done in Spain from the definitions, themes and items created in the nominal group of the SER. This survey was structured in 3 blocks or 3 general topics: block A, efficacy of NSAID (22 items); block B, safety of NSAID (33 items); and block C, special groups (children, older patients, pregnant patients, etc) and other aspects related to NSAID (17 items). The survey was sent through email to all of the members of the SER and could be answered online, by ordinary mail or fax for 1 month. The rheumatologists could add new statements on NSAID if they considered that they represented relevant aspects that had not been included, and should indicate if the relevance of those aspects were based on expert opinion, scientific evidence—providing the corresponding reference—or in the opinion of the rheumatologists themselves.

Afterward, a nominal meeting with experts of the CMR was carried out in which items of the first survey were commented,

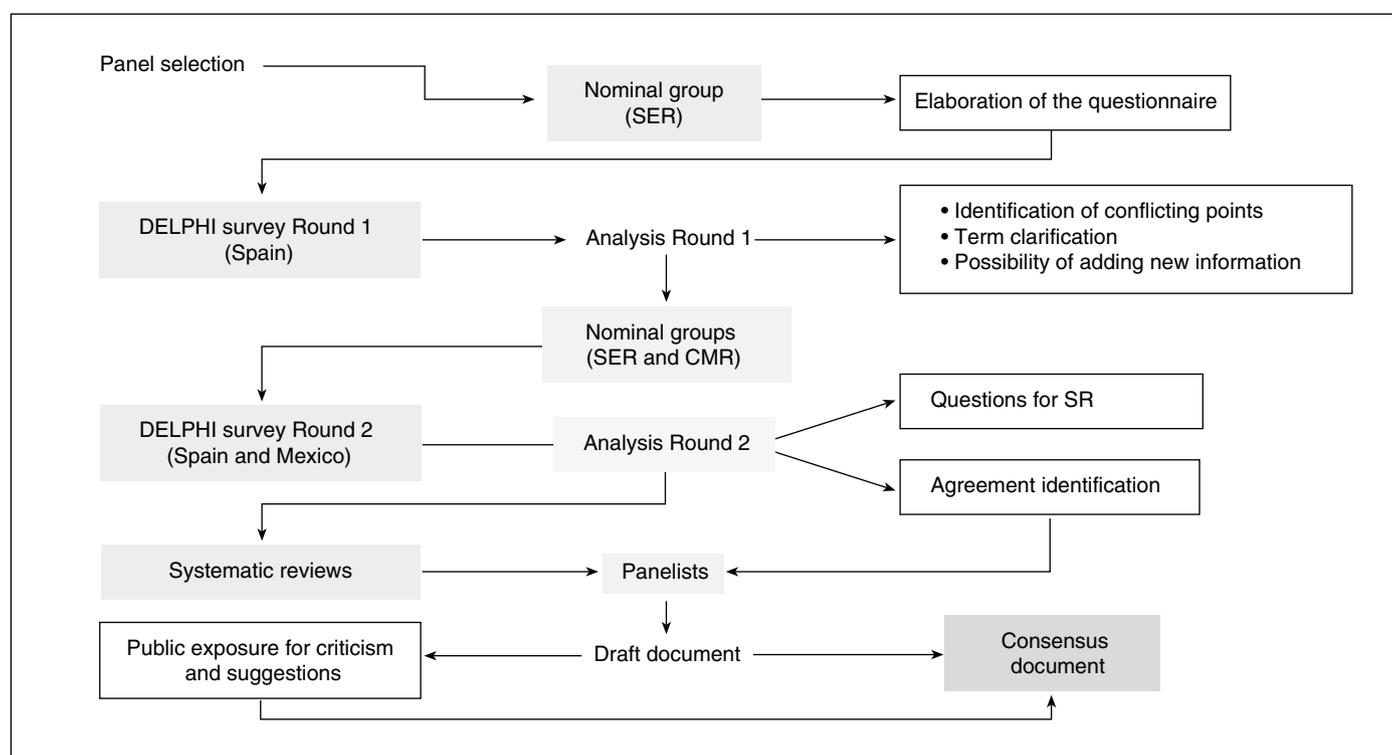


Figure 1. Phases of the methodology used in the elaboration of the consensus document. CMR indicates Mexican College of Rheumatology; SR, systematic review; SER, Spanish Society of Rheumatology.

improved or increased. In a third joint meeting, experts of the SER and CMR unified criteria, selected relevant suggestions of the CMR group and the participants of the first round and added the new items to a second Delphi round. The write up of the items was reviewed in order to adapt them to the language of both countries, improving the recommendations in such a way that they were clear and specific, and eliminating redundant aspects.

The second Delphi survey was structured only in 2 blocks: efficacy of NSAID (26 items) and safety of NSAID (64 items). The survey was sent and responded both in Spain and Mexico during the months of July and August 2007, in the same way as the first round.

Analysis and Consensus Definition

The Delphi surveys were performed in 2 phases, qualitative and quantitative. In the first round, the qualitative analysis consisted in grouping and classifying the comments and proposals of the items that the participating rheumatologists had sent. In 17 cases the reason on which the proposed recommendation was based was explicit: 5 cases experience or personal opinion, 7 based on the opinion of expert groups, and 5 on the literature, although only 2 cases cited the reference. In the second round there was no option to include items or comments.

The quantitative phase in both rounds consisted in calculating the mean (standard deviation) of the scores given by the panelists to each item, as well as the percentage of responses with a low (values 1 or 2), medium (value 3), or high (value 4 or 5) score on the Likert scale which was employed. "Agreement" was defined as a mean score = 4 for an item and "disagreement" when the score was = 2. In both cases, agreement and disagreement, there was consensus for or against. An item was considered conflictive, and therefore no consensus could be reached, when: a) responses were distributed among all of the possible scores from 1 to 5; b) scores were polarized on both sides of the scale; or c) most of the scores were on the middle point of the scale.

After the analysis of the second Delphi round, recommendations which had at least 65% consensus were kept and a list of conflicting recommendations was generated, on which it was necessary to perform a systematic review.

Systematic Reviews

Based on conflicting items, experts formulated questions that could be approached through a systematic review. Not all of the questions were susceptible to being approached in this manner because of the need to adjust to a limited timeline, budget and personnel, leading the panelists to established priorities in the questions using a 1 to 10 scale and the reviewers based the feasibility namely on the performance of an initial search and the allotted time, which was 1 month per systematic review. The methodology employed, including the selection criteria, is detailed in the corresponding reviews, and a short summary of the results is made in the recommendation they are backing.

Final Recommendations

Final recommendations were written from the items in the second Delphi round. Several items were grouped for some of the recommendations because the items were intentionally short and concrete to facilitate the response of the participants. Items on which there was consensus were written in an inverse sense in the final document.

The degree of agreement was defined as the percentage of consensus among those surveyed, as given by the second Delphi round, both in favor and against. When the recommendation included more than 1 item, the score was the average of those given to the different items included in the recommendation.

The level of evidence and the degree of recommendation were classified according to the levels of evidence and recommendation of the Center for Evidence Based Medicine at Oxford.¹⁵ In the case that a recommendation was established from 2 or more affirmations,

both the level of evidence as well as the degree of recommendation that were assigned to the recommendation was the lowest possible.

A draft of the final document was exposed and subjected to comments or modifications by the members of both scientific societies during the month of April 2008.

From this document, an algorithm was developed using MindManager® 7 Pro software.

Results and Discussion: Consensus on the Appropriate Use of NSAID in Rheumatology

This consensus document has as an objective the appropriate use of NSAID in rheumatic diseases and is directed, therefore, to all health professional that are in a situation of using them in their daily clinical practice.

Definition of NSAID

NSAID are drugs with a heterogeneous chemical structure that share antipyretic, anti-inflammatory, and analgesic activity through their capacity of inhibiting the production of proinflammatory prostaglandins.¹⁶ The term NSAID in the recommendations makes reference to traditional NSAID as a whole, coxibs and acetylsalicylic acid (ASA) at anti-inflammatory doses. If any affirmation refers to only to traditional NSAID, coxib or ASA, it will so specify in the corresponding recommendation. Other analgesic NSAID such as lysine clonixylate or metamizole are not included among them.

Definitions of Usage Situations

The use of NSAID can vary according to the rheumatic disease or the moment in the rheumatic process in which they are needed.

Because of this, and with the intention of simplifying the multiple possibilities of use, differentiation is made between acute processes (ie, gout attacks, acute back pain, trauma, etc) and chronic processes, which are divided in mechanical (osteoarthritis) or inflammatory (rheumatoid arthritis, spondyloarthropathies, systemic lupus erythematosus, etc).¹⁷

Definitions of Groups at Risk for Toxicity

Table 1 shows different risk groups and the subclassification of the gastric and cardiovascular risk profiles.

Respecting gastrointestinal risk, it is important to take into account that many of the rheumatic patients have more than one of the enumerated risk factors, especially those undergoing chronic treatment with NSAID. In this sense, it is recognized that the longer the treatment, the more the exposure and, even if the risk remains constant, probability increases. The added risk for the concomitant use of steroids was the object of a systematic review,¹⁸ and it was finally decided to not include it among the risk factors. Both the classification as well as the risk factors in Table 1 refers to gastroduodenal risk (not including the lower gastrointestinal tract).

As for the definition of cardiovascular risk, the process was complicated because there currently is more than one definition and it is evaluated through complex equations. Probably the most employed are the SCORE cardiovascular risk index, which is calculated through an equation in which variables are added and goes from 0 to 70,^{19,20} and the modification of the Framingham equation, in which the variables are adjusted to a series of tables. Both indexes are validated in the Spanish population.²¹ In these indexes the probability of another cardiovascular ischemic event happening is evaluated. Because these indexes are difficult to calculate, the panel preferred to list the included risk factors,

Table 1
Recommendations for the Appropriate Use of NSAID in Rheumatology

Toxicity	Risk Factors	Risk Profile
Gastrointestinal toxicity	History of complicated peptic or gastroduodenal ulcer Use of anticoagulants History of uncomplicated peptic or gastroduodenal ulcer Age >65 years Concomitant use of more than one NSAID (including ASA as antiaggregant) Treatment with high dose NSAID and prolonged duration of NSAID treatment	High gastrointestinal risk: – History of complicated ulcer – or use of anticoagulants – or a combination of 2 or more of the remaining risk factors Moderate gastrointestinal risk – Non-anticoagulated patients, no history of complicated ulcer but with any isolated risk factor Low gastrointestinal risk – Patients with risk factors
Cardiovascular toxicity	Risk factors: – History of cardiovascular events – Diabetes mellitus – Smoking – Hypertension – Hipercholesterolemia/dyslipidemia Associated or modifying factors: male gender, age over 60, active systemic lupus erythematosus, or rheumatoid arthritis	High cardiovascular risk – Patients with a history of cardiovascular events – or diabetics – or high levels of any risk factor, especially in the presence of associated or modifying factors – or with more than one risk factor, especially in the presence of associated or modifying factors Moderate cardiovascular risk factors – Patients with a single risk factor—except in defined situations defined above as high risk—, especially in the presence of associated factors Low cardiovascular risk – Patients without risk factors
Renal toxicity	Renal failure Atherosclerotic renal disease Diabetes mellitus Volume depletion Age >60 years Concomitant use of diuretics Liver cirrhosis	
Liver toxicity	Liver cirrhosis Alcoholism Concomitant use of hepatotoxic drugs	

differentiating between those with more weight (risk factors) and other that, while increasing cardiovascular risk, contribute to the total risk in a lesser way, concretely systemic lupus erythematosus or rheumatoid arthritis, particularly when there is clinical activity and the C-reactive protein concentration is elevated. Therefore, risk factors were established which were adaptable to the daily rheumatology practice based on the above mentioned indexes, which were then consented and approved in the 2 rounds of the Delphi study. Probably, with this attitude, practicality is gained at the expense of precision. Therefore the panel recommends that, in case of doubts, the indexes mentioned above be employed to evaluate cardiovascular risk in a more precise manner.

Renal²² and hepatic risk factors were also established.

Recommendations

The profile of the surveyed in the 2 Delphi rounds and a summary of the results are shown on Table 2. The level of evidence, the degree of recommendation, and the degree of agreement of each recommendation is shown on Table 3. The elaborated recommendations are detailed and nuanced in the lines below. Figure 2 contains a summary algorithm of these recommendations.

Table 2

Results of 2 Delphi Rounds: Profile of Those Surveyed and Aclarations Concerning Analysis

	Round 1 (Spain) (n=35)	Round 2 (Spain and Mexico) (n=95) ^a
Participant characteristics		
Age, mean (interval), y	44 (30-61)	46 (29-75)
Women, n (%)	24 (68)	62 (67)
Years of practice, mean (interval)	17 (5-32)	18 (1-50)
Patients seen in 1 month, mean (interval)	145 (15-500)	241 (15-900)
Health sector they belong to, n (%):		
Public	24 (68)	45 (42)
Private	3 (8)	12 (11)
Both	8 (22)	40 (37)
Summary of results		
Total evaluated items	72 ^b	90 ^c
Agreement, mean (interval), %	60% (31-93)	84% (28-97)
High agreement (≥80%), n (%)	37 (51)	67 (74)
Conflicting items, n (%)	31 (43)	19 (21)
Items included for panel discussion	17	0

^a 62 of SER and 31 of CMR.

^b 22 efficacy, 33 safety, and 17 other aspects.

^c 26 efficacy, 64 safety.

Table 3

Recommendations for the Appropriate Use of NSAID in Rheumatology

Recommendation	DA	LE	DR
A. Recommendations on indication and dosage			
1 NSAID in general can be recommended to treat pain and inflammation in rheumatology; however, there is great variability in the individual response to NSAID, making individualization necessary for the use of any NSAID	94	4	D
2 It is not recommended to use 2 or more simultaneous NSAID because their concomitant use does not increase efficacy and does increase toxicity	94	1b	A
3 No NSAID can be recommended over another based on efficacy (concretely, the efficacy of traditional NSAID is similar to coxibs). Topical route is less effective than orally	80	1b	A
4 In acute processes, NSAID must be employed for the shortest possible period of time at the maximum tolerated dose enough to be effective	90	4	D
5 In chronic processes, NSAID should be used at the minimal necessary dose to maintain a favorable clinical response, evaluating risk factors for adverse events; in addition, the indication for the use of NSAID in a periodic manner must be reevaluated in relation to clinical response and adverse events	94	4	D
6 In rheumatoid arthritis, NSAID will be employed in a concomitant manner with disease modifying anti-rheumatic drugs (DMARD). Once the DMARD function, NSAID will be reduced until suspension if the progression of symptoms allows it	91	4	D
7 In mechanical processes, other treatments must be tried (non pharmacologic, analgesic and osteoarthritis modifying drugs) in order to minimize the use of NSAID	83	1a	A
B. Recommendations regarding toxicity			
b.1. Gastrointestinal risk			
8 The baseline gastrointestinal risk profile of the patient and the NSAID to be used must be evaluated, in such a way as to: – In patients with high gastrointestinal risk, the use of NSAID must be avoided whenever possible and, in case of it being necessary, use coxib + proton pump inhibitors (PPI) – In patients with moderate gastrointestinal risk, coxib by themselves or traditional NSAID + PPI can be used with equal safety – In patients with low gastrointestinal risk, PPI must be employed in case of NSAID related dyspepsia	87	4	D
b.2. Cardiovascular risk			
9 The baseline cardiovascular risk of the patient and NSAID to be used must be evaluated, taking into account fundamental factors such as time and dose in such a way that: – In patients with a high cardiovascular risk the use of NSAID must be avoided. Exceptionally, they can be employed for a limited amount of time and at the lowest possible dose. – In patients with moderate cardiovascular risk, NSAID can be used at a low dose during the shortest possible time	89	4	D
10 In patients with congestive heart failure, edema or uncontrolled hypertension, NSAID should be restricted; isolated hypertension is not a contraindication for the use of NSAID, although its control is necessary during treatment	91	4	D
11 In anticoagulated patients the use of NSAID should be restricted. The use of non pharmacologic methods is recommended as a first choice (rest, weight reduction, use of a cane, rehabilitation), paracetamol or codeine	89	4	D
b.3. Other risks (renal, hepatic, etc)			
12 In patients with renal risk factors the use of NSAID should be restricted	94	4	D
13 In patients with liver disease, NSAID should be used at the minimum necessary dose for the shortest possible time and with a determination of liver enzymes; in patients with severe hepatic insufficiency their use is contraindicated	85	4	D
14 In patients with a history of hypersensitivity to NSAID, erythema multiforme, urticaria, Stevens-Johnson syndrome or photosensitivity, caution must be taken when prescribing an NSAID	94	4	D
15 Caution must be taken when using NSAID in asthmatic patients	90	4	D
16 When there is a history of allergy to traditional NSAID or aspirin, precautions must be taken because evidence is contradictory regarding cross-reactions with other NSAID	86	4	D
17 In hematological processes, NSAID should be used at the minimal necessary dose for the shortest possible time and a blood count must be taken	78	4	D
18 In patients with systemic lupus erythematosus, the appearance of aseptic meningitis must be considered in relation to the use of NSAID, in particular ibuprophen	73	4	D

Abbreviations: DA, degree of agreement; DR, degree of recommendation; EL, level of minimal evidence in the recommendation.

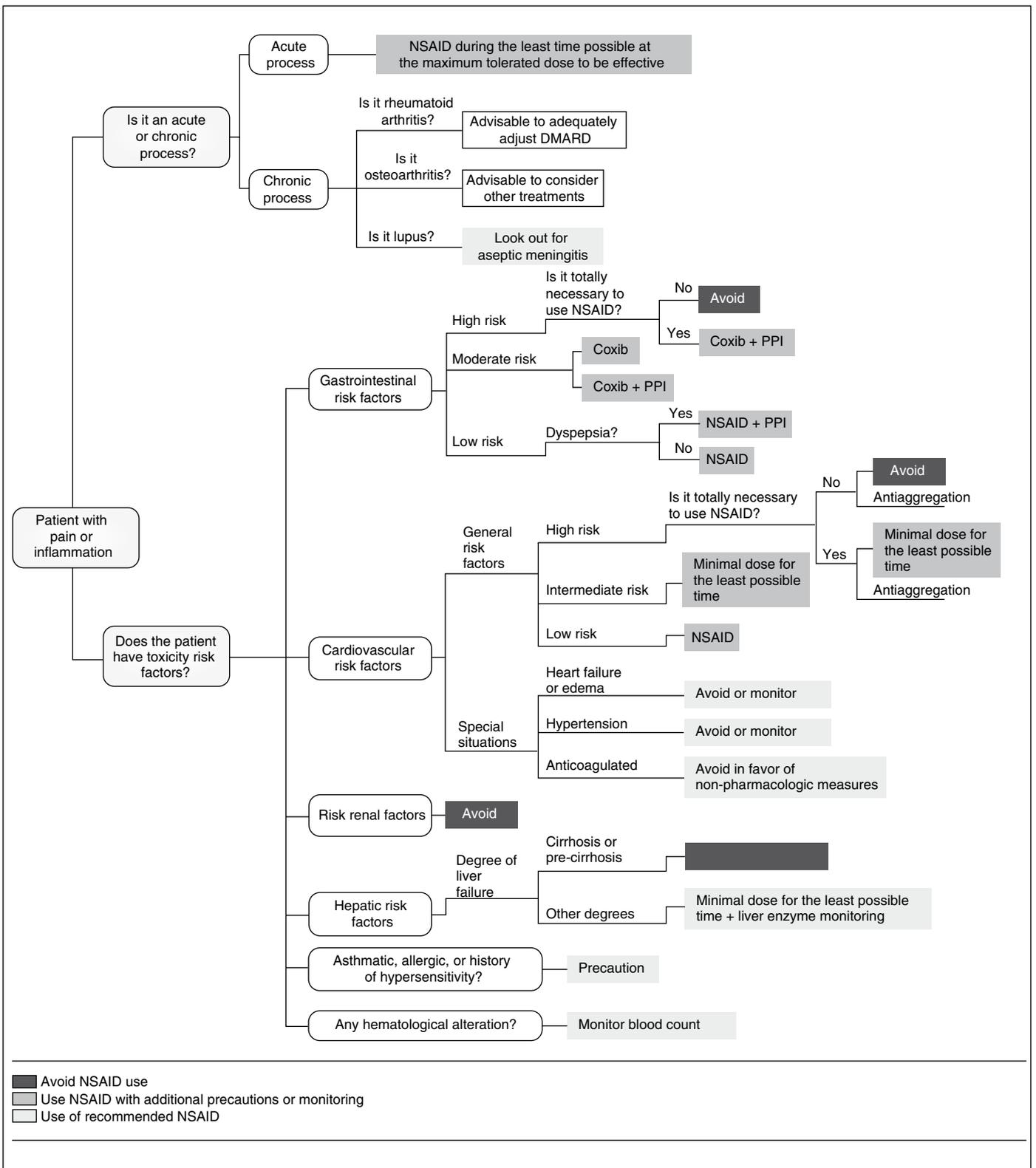


Figure 2. Algorithm of the appropriate use of non-steroidal anti-inflammatory drugs (NSAID) in rheumatology. DMARD indicates disease modifying anti-rheumatic drug; PPI, proton pump inhibitor

1. NSAID in general can be recommended to treat pain and inflammation in rheumatology; however, there is a great variability in responses to NSAID, making it important to individualize every treatment.

Numerous studies demonstrate the efficacy of NSAID in the reduction of bone and muscle pain. There are less studies, also

positive, that have a reduction in inflammation as an outcome measure. All of them are clinical trials and, therefore, evidence level 1. But the recommendation on the individual response to NSAID is an appreciation of clinical practice or indirect evidence of observational studies,²³ which in any case reduced the general level of evidence and the degree of recommendation, although the

agreement level is very high (96% for efficacy and 92% for variability-individualization). According to the results of 2 systematic reviews that the panel requested, NSAID have, in general, the same efficacy in all age groups.^{24,25}

2. It is not recommendable to use 2 or more NSAID simultaneously, because concomitant use does not increase efficacy and in turn increases toxicity.

No review of evidence was carried out because the consensus in this regard was very high.

3. No NSAID can be recommended over another in any case, based on efficacy—concretely, the efficacy of traditional NSAID is similar to coxib—. The topical route is less effective than the oral route.

This affirmation obtained a lesser degree of agreement (78%). The expert committee concluded that there is evidence in at least one meta-analysis⁷ and more than one controlled clinical trial on the coxib's and the traditional NSAID similar efficacy in osteoarthritis,²⁶ rheumatoid arthritis, gout,²⁷ and ankylosing spondylitis.²⁸ The degree of evidence to say that efficacy is similar is therefore grade 1a or 1b.

Regarding the administration route of NSAID, there is evidence that shows that they are more effective than when administered orally than topically, especially in osteoarthritis of the knee, based on a level 1b study.²⁹ Toxicity of NSAID when NSAID are used rectally, intramuscular, or intravenously is similar to that that occurs when employed orally, something important when dealing with gastrointestinal toxicity.

4. In acute processes, NSAID should be used for the least time possible at the maximum tolerated dose enough to be effective.

This recommendation is the product of the recognition of their efficacy, but also their toxicity.

5. In chronic processes, NSAID should be used at the minimal necessary dose to maintain a favorable clinical response, evaluating risk factors for adverse events; in addition the indication for the use of NSAID periodically should be reassessed periodically in relation to the clinical response and adverse events.

The degree of agreement was high (94%) and once again based on the balance between risk and benefit (evidence level 1). Members of the panel coincided (85% agreement) that seronegative spondyloarthropathies frequently need the use of high doses for long periods of time, and that in these patients the benefits outweigh the risks. In this last case, the level of evidence backing this recommendation is 4.

6. In rheumatoid arthritis, NSAID will be used together with disease modifying drugs (DMARD). Once the DMARD act, NSAID shall be reduced until their cessation if progression of the symptoms allows it.

The use of DMARD must be put before the use of NSAID and relegate the latter to control of symptoms only.

7. In mechanical processes, other treatments—non pharmacologic therapies, analgesics, osteoarthritis modifying drugs (slow acting agents)—should be considered to minimize the use of NSAID.

The reduced agreement can be explained by the marginal size of the effect of treatments for osteoarthritis with other, non-NSAID drugs, concretely glucosamine, chondroitin sulfate, or dyacerein,²⁹ or by the also reduced effect and the need for interruption due to adverse events of treatment with tramadol.³⁰ It must be pointed out also that the intra-articular infiltration with steroids or hyaluronic acid are other measures that are recommended as NSAID substituted in the treatment of knee osteoarthritis, according to each individual case.^{31,32}

8. The baseline gastrointestinal risk profile of each patient and the NSAID to be employed must be estimated in such a way as to:

8.1. In patients with a high gastrointestinal risk, the use of NSAID must be avoided whenever possible, and in case they are needed, it is recommended to use coxib + proton pump inhibitors (PPI).

8.2. In patients with a moderate gastrointestinal risk coxibs can be used by themselves or traditional NSAID + PPI with equivalent safety.

8.3. In patients with a low gastrointestinal risk, PPI must be employed in case they present NSAID-associated dyspepsia.

Participants pointed out to a clear need to evaluate the gastrointestinal risk profile (95% agreement) and for using coxib + PPI in patients with a high risk (89%). However, in the recommendations for moderate (83%) and low (77%) risk, the agreement was less. Upon discussion, it is evident that the main problem when assuming these affirmations and translating them to the daily clinical practice is cost. In the case of moderate risk, the cost of preventing a severe gastrointestinal event or one with clinical repercussion is, for the patient, elevated. In such a circumstance, it is important to individualize the use of PPI. The same happens with recommendations when the risk is low, because treatment for NSAID associated dyspepsia is costly. The rheumatologist must consider the optimal balance between recommendations and cost. Panelists also considered important to point out that the elimination of *Helicobacter pylori* does not suppress the need for PPI in those patients at risk.

These recommendations refer to the gastric and duodenal risk factor. Panelists are aware that no recommendations were made for possible complications in the lower gastrointestinal tract, which can be associated to NSAID. Although this is a real problem, the lack of agreement in the Delphi survey and the difficulty to establish risk levels based on the available evidence makes it necessary to postpone any recommendation to this end for a future review of the consensus.

Steroids are normally included among the risk factors for a gastrointestinal complication. Because the concomitant use of steroids and NSAID is common in rheumatology, a systematic review on the incidence of severe gastrointestinal events associated to the combined use of steroids and NSAID was carried out.^{18,33} The review showed that the incidence of complications is very low (evidence level 3), leading the panel to consider that the concomitant use of steroids does not constitute a gastrointestinal risk factor.

The appearance of gastrointestinal adverse events in children is similar to that found in adults and similar to all NSAID except aspirin, which carries a higher risk²⁴—probably in relation to the higher doses used in rheumatology—. In the elderly, although it is not easy to say from what age, the risk of gastrointestinal complications seems higher, although it must be taken into account that PPI, which are used less in this population, are equally effective than at younger ages.²⁵

9. The baseline cardiovascular risk profile of the patient and the NSAID must be evaluated, taking into account that the fundamental factors are time and dose, in such a way as to:

9.1. In patients with high cardiovascular risk, the use of NSAID must be avoided. They can exceptionally be employed for a limited time and at the lowest possible dose.

9.2. In patients with intermediate cardiovascular risk, NSAID can be used at a low dose during the shortest possible time period.

As happens with the gastrointestinal risk, it is important to estimate the cardiovascular risk of each patient and know that, upon longer durations of treatment and higher NSAID doses, the risk is increased (evidence level 4, recommendation degree D). The probability that a new cardiovascular event occurs or an existing one is worsened is elevated significantly in patients with high cardiovascular risk, making the use of therapeutic alternatives different from NSAID preferable (91% agreement, evidence level 4; recommendation degree D). In addition, according to the management guidelines for the prevention of cardiovascular risk, the panel recommends (84%) that all of the patients with high cardiovascular risk receive platelet antiaggregants.³⁴ Because no NSAID equals the antiaggregant role of ASA or an equivalent drug, in patients with this indication, this shall not be suspended when any anti-inflammatory is concomitantly administered.

The recognition of the cardiovascular risk associated to coxib versus placebo led to doubts on the cardiovascular safety of traditional NSAID. It is currently recognized that coxib have a larger cardiovascular risk when compared to placebo, but their cardiovascular risk profile is similar to that of diclofenac,¹⁰ which is admitted with high agreement (90%) and based on a 1b evidence level. In any case, the panel (90%) wants to state that traditional NSAID are not exempted from cardiovascular risk (level 1b, recommendation A). There is isolated evidence that the cardiovascular profile of naproxen could be more beneficial than that of other NSAID,³⁵ even if the panel decided not to establish any specific recommendations in the absence of a determined systematic review.

In case an NSAID had to be prescribed to a diabetic patient under control with oral hypoglycemic drugs, the panel doubted on the interaction with NSAID, and therefore a systematic review was carried out.³³ The review proved, with a level of evidence 2, that no proof exists that glycemic control is affected in patients under treatment with oral antidiabetic drugs or insulin and NSAID.

There are no cardiovascular toxicity studies in children.²⁴ Age, in the absence of risk factors, does not increase the cardiovascular risk of NSAID.²⁵

10. In patients with congestive heart failure, edema, or uncontrolled hypertension, NSAID use must be restricted; isolated hypertension is not a contraindication for NSAID use, but its controlled is indicated during the treatment.

In these cases, common in daily practice, the cardiovascular risk profile should be established beforehand and the pertinent recommendations should be applied according to said risk. When these affection coexist, it is recommended to carefully evaluate the indication, avoid the use of NSAID whenever possible, use the lowest dose for the shortest time period possible, use the lowest dose during the shortest time and establish pertinent follow up measures (90% agreement; evidence level 4, degree of recommendation D).

11. The use of NSAID should be restricted in anticoagulated patients. It is recommended that non-pharmacologic measures be used as a first line response—rest, weight reduction, use of a cane, rehabilitation—, as well as paracetamol or codein.

The association between anticoagulation or antiaggregation and NSAID increases gastrointestinal and bleeding risk in general^{37,38} (evidence level 3b). On the other hand, anticoagulated patients usually have an elevated cardiovascular risk profile. Because the rheumatologist in the daily clinical practice is confronted with this situation, there are doubts as to which NSAID is the best. Some publications talk about certain safety in the use of coxib in those circumstances.^{39,40} In spite of that, a specific recommendation is not established because there was a lack of agreement on the Delphi survey.

12. In patients with renal risk factors, the use of NSAID must be restricted.

Among the patients with subacute renal failure, approximately 8% developed it due to NSAID use.²² NSAID suitable for use in patients with renal risk factors was one of the topics subjected to systematic review.⁴¹ Most of the studies identified only analyzed coxib, because the evidence on the renal safety profile of the other NSAID was limited. In general, a prudent management of the renal problem is suggested both with conventional NSAID and coxib, looking out for possible adverse events.

13. In patients with liver disease, NSAID should be used at the minimal dose possible for the least amount of time and with a determination of liver enzymes; in patients with severe liver failure, use is contraindicated.

14. In patients with a history of allergy to NSAID, erythema multiforme, urticaria, or Stevens-Johnson's, or photosensitivity, precaution must be used when prescribing NSAID.

There is no evidence on what to do in the case of prescribing NSAID to patients with previous hypersensitivity, so no precise recommendations, only general ones, can be established.

15. Caution is recommended when using NSAID in asthmatic patients.

16. When a history of allergy to traditional NSAID or ASA is present, precautions must be taken because there is contradicting evidence of cross-reactions to other NSAID.

17. In hematologic processes, NSAID should be used at the lowest possible dose for the shortest time possible and a complete blood count must be performed.

18. In patients with systemic lupus erythematosus, the possibility of aseptic meningitis must be considered when using NSAID, especially ibuprophen.

In patients with lupus, there have been case reports of aseptic meningitis associated to ibuprophen use, although some cases report other NSAID.⁴² The classic presentation of aseptic meningitis induced by NSAID includes fever, headache, and neck rigidity that appear from a few minutes to several hours after ingesting the drug. The clinician must always rule out an infectious cause.

Additional Comments

This consensus document is an effort on the part of rheumatologists from 2 countries to unify criteria in relation to NSAID. Its strength resides in the methodology employed—nominal groups, Delphi methods, and evidence reviews—, developed specifically to insure the adaptation of the recommendations. However, the adaptation of both panels from different countries and the fact that they could not always meet obviously has bearing on the final document.

Because rheumatic diseases are a very heterogeneous group of disease, it was expected that the recommendations would fall victim to that heterogeneity. As with all recommendations, these are subject to improvement. Maybe the users will find the lack of drug names a fault. However, there really is no evidence that suggests that any concrete NSAID could be considered as prominent in any recommendation. On the other hand, NSAID available or authorized on one or the other side of the Atlantic can vary, as well as their cost, making concrete recommendations not suitable for their complete application by both scientific associations.

It is important to comment on paracetamol. During the expert discussion and the Delphi questionnaires, agreement between physicians was high with regard to the fact that this drug is analgesic at low dose (<2 g/day) and shares NSAID toxicity at high dose (>3 g/day). Therefore, if high doses are used, as recommended by the ACR for the treatment of osteoarthritis or patients with inflammatory disease, their gastrointestinal toxicity, which is similar to an NSAID, must be taken into account.

A review of the evidence for the use of NSAID in pregnant patients was also undertaken. Evidence obtained was scarce, but the studies reviewed point to an increase in teratogenicity, premature births, or abortions,⁴³ and the use of NSAID should be avoided not only at the end of the pregnancy but also during its first months.

In general, the recommendations are directed to a use of NSAID that reduces the possibility of toxicity to the bare minimum, both gastrointestinal and cardiovascular as well as others, not forgetting special groups, and also to make a more rational use of these drugs, in such a way that in some cases, different and less toxic treatment measures are recommended.

Conclusions

NSAID are drugs that are recommended to treat pain and inflammation in rheumatic disease. Multiple variations in the risk profiles of the patients and the difference that exist between the drug molecules make it necessary to individualize their use in relation to the type of process for which they are employed and the patient's characteristics. NSAID should be used, as long as the

disease allows it, for short periods of time and at the lowest possible dose, always within their efficacy range and looking out specifically for digestive, cardiovascular, renal, hepatic, and hematologic complications.

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Conflicts of Interest

Belongs to a board of consultants: Luis Alberto García Rodríguez (Pfizer), Ángel Lanás Arbeloa (Pfizer, Astra-Zéneca), Rolando Espinosa (Pfizer, Roche), Blanca Hernández Cruz (BMS), Hilario Ávila Armengol (MSD).

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