Applied Medical Informatics
Original Research Vol. 31, No. 3/2012, pp: 37-46

Non-steroidal Anti-inflammatory Drugs Ranking by Nondeterministic Assessments of Probabilistic Type

Luiza Mădălina MOLDOVEANU, Ştefan ŢIGAN, and Andrei ACHIMAŞ CADARIU

"Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, 6 Louis Pasteur, 400349 Cluj-Napoca, Cluj, Romania.
E-mail: luiza.moldoveanu@gmail.com

* Author to whom correspondence should be addressed; Tel.: +4-0264-279722

Received: 20 August 2012 / Accepted: 10 September 2012 / Published online: 12 September 2012

Abstract
With a number of common therapeutic prescriptions, common mechanisms, common pharmacological effects - analgesic, antipyretic and anti-inflammatory (acetaminophen excepted), common side effects (SE) (platelet dysfunction, gastritis and peptic ulcers, renal insufficiency in susceptible patients, water and sodium retention, edemas, nephropathies), and only a few different characteristics – different chemical structures, pharmacokinetics and different therapeutic possibility, different selectivities according to cyclooxygenase pathway 1 and 2, non-steroidal anti-inflammatory drugs (NSAIDs) similarities are more apparent than differences. Being known that in a correct treatment benefits would exceed risks, the question "Which anti-inflammatory drug presents the lowest risks for a patient?" is just natural. By the Global Risk Method (GRM) and the Maximum Risk Method (MRM) we have determined the ranking of fourteen NSAIDs considering the risks presented by each particular NSAID. Nimesulide, Etoricoxib and Celecoxib safety level came superior to the other NSAIDs, whereas Etodolac and Indomethacin present an increased side effects risk.

Keywords: NSAIDs ranking; NSAIDs side effects (SE); Ranking methods; Global Risk Method; Maximum Risk Method

Introduction

Non-steroidal Anti-inflammatory Drugs (NSAIDs) have three major effects: antipyretic, analgesic and anti-inflammatory (acetaminophen excepted), and have other effects considered secondary: inhibition of uterine contractions (tocolytic effect), the effect of closing the persistent ductus arteriosus in neonates (indomethacin), decreased intestinal peristalsis, reduced risk of certain types of cancer (colorectal cancer, breast cancer - celecoxib), antiplatelet effect (cardiology dose aspirin 75-325 mg/day, indomethacin, phenylbutazone) and each of them are not equally potent in these actions [1]. NSAIDs also share the same side effects: cutaneous [2,3], hepatic [4-6], renal [7-10], gastrointestinal [11-14], musculoskeletal SE [4,15], cardiovascular [4, 16-19], respiratory, urinary, nervous [4].

NSAID ranking according to their implied risk is extremely useful, representing an evaluation of the same according to their possible impact on the patient. Side effects of drugs are gathered according to six categories [20]: dose-dependent, dose-independent, administration-time-dependent, dose-dependent and administration-time-dependent, abandon (giving up treatment because of side

effects) and treatment failure (because of inefficiency). In this article we determined a NSAID ranking considering risk-type criteria.

Material and Method

We have considered the following fourteen non-steroidal anti-inflammatory drugs (random order): Celecoxib, Ibuprofen, Naproxen, Etoricoxib, Diclofenac, Ketoprofen, Indomethacin, Nimesulide, Piroxicam, Meloxicam, Acetaminophen, Ketorolac, Etodolac, Tenoxicam.

In order to gather all the relevant information we have used meta-analysis type studies or original articles selected by means of MEDLINE search engine based on key words (non-steroidal anti-inflammatory drugs, side effects, efficiency, gastrointestinal side effects, cardiovascular side effects, nephrotoxicity, hepatotoxicity, cutaneous side effects, musculoskeletal side effects, Celecoxib, Ibuprofen, Naproxen, Etoricoxib, Diclofenac, Ketoprofen, Indomethacin, Nimesulide, Piroxicam, Meloxicam, Acetaminophen, Ketorolac, Etodolac, Tenoxicam). Finally we have selected those studies containing information related to the number of patients include in the survey and the number of side effects generated by the administration of a NSAID [4, 16-19, 21-65].

We have used the risk-type criteria, representing the probability that the patient may develop a side effect (SE): cutaneous, gastrointestinal, hepatic, respiratory, renal, urinary, cardiovascular, nervous, musculoskeletal, severe cardiovascular risk (myocardial infarction, stroke and sudden cardiac death), treatment failure (inefficiency) and abandon.

The ranking complexity increases as soon as several ranking options appear, depending on a great number of criteria that may be in conflict, at the same time increasing the number and the nature of uncertainty factors. Criteria are separately assessed and they must be independent from one another.

Applying the independence algorithm based on the Pearson correlations we have obtained the following criteria: cutaneous SE, gastrointestinal SE, hepatic SE, renal SE, cardiovascular SE, nervous SE, musculoskeletal SE, severe cardiovascular risk and Inefficiency.

Global Risk Method (GRM)

An assessment of each NSAID is displayed below by estimating risk probability for one of $A_1,A_2,...,A_n$ ailments presumed independent. Therefore, for each NSAID, the risk to develop at least one of $A_1,A_2,...,A_n$ ailments is assessed according to the following formula:

(1) $F(\text{NSAIDs}) = Pr_s(A_1 \cup A_2 \cup ... \cup A_n)$

where

(2) $$Pr_s(A_1 \cup A_2 \cup ... \cup A_n) = \sum_{i=1}^{n} Pr_s(A_i) - \sum_{i \neq j=1}^{n} Pr_s(A_i \cap A_j) + \sum_{i \neq j \neq k} Pr_s(A_i \cap A_j \cap A_k) - ...$$

In the NSAID assessment we have considered that $A_1,A_2,...,A_n$ ailments are independent, therefore we accept:

$$Pr_s(A_i \cap A_j) = Pr_s(A_i) \times Pr_s(A_j), i \neq j,$$

$$Pr_s(A_i \cap A_j \cap A_k) = Pr_s(A_i) \times Pr_s(A_j) \times Pr_s(A_k), i \neq j \neq k$$

Below we have estimated $F(NSAID_s)$ by calculating the probability of not getting either of the $A_1,A_2,...,A_n$ ailments, namely

$$Pr_s(non(A_1 \cup A_2 \cup ... \cup A_n)) = Pr_s(non(A_1) \cap ... \cap non(A_n))$$

However, based on independence of criteria the following result:

$$Pr_s(non(A_1 \cup A_2 \cup ... \cup A_n)) = Pr_s(non(A_1)) \times ... \times Pr_s(non(A_n)) = (1 - Pr_s(A_1)) \times ... \times (1 - Pr_s(A_n))$$

Therefore NSAID assessment can be made according to the following formula:

(3) $$F(AINS_s) = 1 - (1 - Pr_s(A_1)) \times ... \times (1 - Pr_s(A_n))$$

The Global Risk Method includes the following steps:

Step 1. Risk probabilities are calculated $r_{sj}, s = 1,2,...,14; j = 1,2,...,13$

Step 2. Weighted risk probabilities are determined by weights scale by using the formula:

$v_{sj} = (r_{sj})^{w_j}, s = 1,2,...,m; j = 1,2,...,n$

Step 3. The global risk is estimated for each NSAID by

(3) $F(AINS_s) = 1 - \prod_{j=1}^{n} (1 - v_{sj})$

Step 4. NSAIDs are ranged increasingly according to their global risks.

(4) $F(AINS_s) = 1 - \prod_{j=1}^{n} (1 - v''_{sj})$

Maximum Risk Method (MRM)

In this approach we have considered the following risk criteria: cutaneous SE, gastrointestinal SE, hepatic SE, renal SE, cardiovascular SE, nervous SE, musculoskeletal SE, severe cardiovascular risk and Inefficiency and R SE.

I am going to assess each NSAID by estimating the maximum risk probability for any of A_1,A_2,..., A_n side reactions. By MRM, NSAIDs are ranked in increasing order according to the maximum risk.

The Maximum Risk Method includes the following steps:

Step 1. Risk probabilities are calculated based on data $r_{sj}, s = 1,2,...,14; j = 1,2,...,13$

Step 2. Criteria weights are situated on a scale according to the formula:

$w'_j = \frac{\min\{w_k \mid k = 1,2,...,13\}}{w_j}, j = 1,2,...,13$

Step 3. Risk probabilities are weighted by weights situated in step 2 scale

$v'_{sj} = r_{sj}^{w'_j}, s = 1,2,...,14; j = 1,2,...,13$

Step 4. The maximum risk is estimated for each NSAID by

(5) $F(AINS_s) = \max\{v'_{sj} \mid j = 1,2,...,13\}$

Step 5. NSAIDs are ranged increasingly according to maximum risks, the best being the one with the lowest maximum risk.

Results

Results obtained by Global Risk Method

The resulting ranking in the global risk approach is presented in Table 1, where the global risk for each NSAID is determined by the formula (3).

Table 1. GRM Ranking

No	NSAID	RISK
1	**Nimesulide**	0.227092
2	**Etoricoxib**	0.392118
3	**Celecoxib**	0.430254
4	**Acetaminoafen**	0.489999
5	**Naproxen**	0.504021
6	**Tenoxicam**	0.533404
7	**Ibuprofen**	0.546035
8	**Meloxicam**	0.553035
9	**Piroxicam**	0.568072
10	**Ketorolac**	0.589887
11	**Diclofenac**	0.633493
12	**Ketoprofen**	0.642766
13	**Etodolac**	0.661972
14	**Indometacin**	0.759393

The minimum global risk anti-inflammatory is Nimesulide, closely followed by Etoricoxib and

Celecoxib.

Results Obtained by the Maximum Risk Method

Determining and ranking by order of growth the maximum risk for each NSAID, where the maximum risk is calculated based on formula (5) the following new ranking results in non-steroidal anti-inflammatory drugs:

Table 2. MRM Ranking

No	NSAID	RISK
1	**Nimesulide**	0.1883
2	**Etoricoxib**	0.3004
3	**Celecoxib**	0.3438
4	**Ibuprofen**	0.3642
5	**Acetaminoafen**	0.3652
6	**Piroxicam**	0.3902
7	**Naproxen**	0.3942
8	**Tenoxicam**	0.4345
9	**Diclofenac**	0.4859
10	**Ketorolac**	0.4931
11	**Ketoprofen**	0.4954
12	**Meloxicam**	0.4995
13	**Indometacin**	0.5029
14	**Etodolac**	0.5792

The lowest found minimum risk anti-inflammatory is Nimesulide, closely followed by Etoricoxib and Celecoxib as with the GRM, and the last in the ranking are Etodolac and Indomethacin (in reversed order as compared to GRM)

Table 3. Correlation of results obtained by GRM and MRM approaches

			MRG	MRMX
Spearman's rho	MRG	Correlation Coefficient	1.000	.897**
		p		0.0000025
		N	14	14
	MRMX	Correlation Coefficient	.897**	1.000
		p	0.0000025	
		N	14	14

** Correlation is significant at the 0.01 level (2-tailed).
N - number of alternatives

When comparing GRM and MRM rankings we find a significantly high Spearman correlation($|\varrho| > 0.897$), the two approaches yielding similar rankings, even if the results are different.

Discussion

Pain management represents one of the situations often met by clinicians. The challenge is to find the most efficient treatment, which is the closest to the general clinical information sheet of a patient and generate the least side effects. Used for the management of many symptoms and pathologies, non-steroidal anti-inflammatory drugs continue to be among the widest prescription drug classes in the whole world, being recommended in decreasing pain and the anti-inflammatory process. It is considered that over 30 million people are daily on NSAID medication and about half of them are elderly people [66]. Approximately 25% of the total side effects generated by the

consumption of drugs are caused by NSAIDs, over one hundred thousand hospital admissions being recorded and over 16000 annual deaths caused exclusively by gastrointestinal side effects of NSAIDs [4, 67].

Result accuracy in the ranking issue can be influenced by criteria-related errors, the chosen ranking criterion, as well as by the transcription of initial data and even the number of criteria and alternatives. The ranking process should not include irrelevant criteria or omit relevant ones, as this may also lead to wrong results.

Criteria weight rates represent a subjective factor within the ranking techniques, which may influence the order of alternatives, from one decision maker to another. The relative importance of criteria differ according to the significance awarded by each decision administrator for each and every criterion, meaning that different decision makers may award different degrees of importance to criteria, differently underlining their importance, and this may generate totally different results and, implicitly, conflicts between the rankings of different decision makers.

For example, the weights we have attributed to criteria within the NSAID ranking can be considered non-accurate and disputed by another clinician.

We have considered that treatment failure (due to inefficiency) and abandon (following annoying side effects in a patient) weigh the most in establishing the NSAID ranking, whereas cutaneous and musculoskeletal side effects have been attributed minimum weights by us. For side effects, we have also attributed a high weight to severe cardiovascular events occurred during the NSAID treatment, closely followed by gastrointestinal side effects. Another decision maker might have awarded lower weight to gastrointestinal effects having an increased incidence, and being associated to a large number of hospitalizations.

If probability represents the occurrence probability of an event, the risk represents the chance to produce an unwished event as well as the seriousness of consequences generated by the event. Assessing or estimating the risk resides in risk prioritization.

In order to achieve a NSAID ranking by GRM, we have assessed each of the fourteen non-steroidal anti-inflammatory drugs and estimated the probability of global risk for one of the considered side effects.

The method principle consists of quantifying the risk as the product between risk weight and risk probability, and the safety level will be in reverse proportion to its level. After estimating the global risk for each NSAID, it was easy to range the NSAIDs according to the increasing levels of their global risks, safety profiles of Nimesulide, Etoricoxib and Celecoxib proving superior to the other NSAIDs, whereas Ketoprofen, Etodolac and Indomethacin are more likely to risk side effects.

Non-steroidal anti-inflammatory drugs represent a largely prescribed class of drugs in the symptomatic treatment of pain and inflammation, which is why we should not forget that a part of their side effects are more important and more severe than the ailment for which they have been initially administered. By the Maximum Risk Method we have established a NSAID ranking based on the maximum risk represented by each non-steroidal anti-inflammatory drug for each type of side effect.

On the top of the two rankings there are Nimesulide, Etoricoxib and Celecoxib, Nimesulide confirming a safety profile better than the rest of NSAIDs. Literature data seem to support it as well, therefore resulting that Nimesulide possesses a weak potential for gastrointestinal complications and cardiovacular [23-26,37,41,68,69]. Taking into account all the spontaneous reports of gastrointestinal side effects, Nimesulide has been associated to only half of the number reported for other NSAIDs (Diclofenac, Ketoprofen, Piroxicam)[4]. Compared to Naproxen, its action upon platelet aggregation is insignificant (does not produce bleeding by favoring pro-aggregation TXB2 production and does not generate thromboembolic complications by favoring pro-aggregation PGI2 production) [69].

The fact that we cannot completely eliminate side effects of a treatment, and therapeutic alternatives present more other risks, makes their correct prioritizing an important measure in the medical decision.

As for Etoricoxib, ranking two on minimum risk level, regardless of the method used, five of the seven studies from which we have extracted data upon which the NSAID ranking has been

made, have been either sponsored, or the authors were collaborators of Etoricoxib producer, this aspect making results objectivity a bit doubtful.

Conclusions

Considering the risk of each NSAID, by two separate ranking methods we have determined Nimesulide, Etoricoxib and Celecoxib to have a safety profile superior to the other NSAIDs, whereas Etodolac and Indomethacin present an increased side effects risk.

Beside the fact that they are not large information and time consumers, the Global Risk Method and the Maximum Risk Method can be a useful instrument in therapeutic alternative (NSAID) with the lowest risks.

The results of this study confirm the fact that ranking method approach in the medical field can offer clear advantages in therapeutic decisions.

List of abbreviations (if any)

NSAID	Non-steroidal anti-inflammatory drug
GRM	Global Risk Method
MRM	Maximum Risk Method
SE	Side effects

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Cristea AN. Tratat de farmacologie, Ediţia I, Ed. Medicală Bucureşti, 2005.
2. Lee A. Adverse Drug Reactions (2nd edition). Published by the Pharmaceutical Press; 2006, p. 8-10.
3. Stern RS, Bigby M. An expanded profile of cutaneous reactions to nonsteroidal anti-inflammatory drugs. JAMA 1984; 252:1433-7.
4. Conforti A, Leone R, Moretti U, Mozzo F, Velo G. Adverse drug reactions related to the use of NSAIDs with a focus on nimesulide: results of spontaneous reporting from a Northern Italian area. Drug Saf 2001;24:1081-90.
5. Traversa G, Bianchi C, Da Cas R, Abraha I, Menniti-Ippolito F, Venegoni M. Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. BMJ 2003; 327:18-22.
6. Bessone F. Non-steroidal anti-inflammatory drugs: What is the actual risk of liver damage? World J Gastroenterol 2010;16(45):5651-61.
7. Kristensen SL, Fosbøl EL, Kamper A-L, Køber L, Hommel K, Lamberts M, et al. Use of nonsteroidal anti-inflammatory drugs prior to chronic renal replacement therapy initiation: a nationwide study. Pharmacoepidem. Drug Safe 2012;21:428-34.
8. Delmas PD. Non-steroidal anti-inflammatory drugs and renal function. Br J Rheumatol 1995;34 (suppl 1):25-8.
9. Griffin MR, Yared A, Ray WA. Nonsteroidal antiinflammatory drugs and acute renal failure in elderly persons. Am J Epidemiol 2000;151(5):488-96.
10. Ejaz P, Bhojani K, Joshi VR. NSAIDs and Kidney. JAPI 2004;52:632-9.
11. Kim HC, Lee MC, Moon YW, Seo SS, Lee KW, Lee JH, Choi CH. The Pattern of Use of Oral NSAIDs with or without Co-prescription of Gastroprotective Agent for Arthritic Knee by

Korean Practitioners Knee Surg Relat Res 2011;23(4):203-7.
12. Lanza FL, Chan FK, Quigley EM. Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol 2009;104:728-38.
13. Henry D, Lim LL, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, et al. Variability in risk of gastrointestinal complications with individual non-steroidal antiinflammatory drugs: results of a collaborative meta-analysis. BMJ 1996;312:1563-6.
14. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med. 2001;345:433-42.
15. Musculoskeletal adverse drug reactions: a review of literature and data from ADR spontaneous reporting databases. Current Drug Safety 2007;2:47-63.
16. Gislason GH, Jacobsen S, Rasmussen JN, Rasmussen S, Buch P, Friberg J, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. Circulation 2006;113(25):2906-13.
17. Hegazy R, Alashhab M, Amin M. Cardiorenal Effects of Newer NSAIDs (Celecoxib) versus Classic NSAIDs (Ibuprofen) in Patients with Arthritis. Journal of Toxicology 2011: 862153 (doi: 10.1155/2011/862153).
18. Chang DJ, Desjardins PJ, King TR, Erb T, Geba GP. The analgesic efficacy of etoricoxib compared with oxycodone/acetaminophen in an acute postoperative pain model: a randomized, double-blind clinical trial. Anesth Analg 2004; 99:807-15.
19. Cheetham TC, Graham DJ, Campen D, Hui R, Spence M, Levy G, et al. Myocardial Infarction and Its Association with the Use of Nonselective NSAIDs: A Nested Case-Control and Time-to-Event Analysis. Perm J 2008;12(1):16-22.
20. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management Lancet 2000;356(9237):1255-9.
21. Bingham CO III, Sebba AI, Rubin BR, Ruoff GE, Kremer J, Bird S, et al. Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies. Rheumatology (Oxford). 2007;46(3):496-507.
22. Chang CH, Shau WY, Kuo CW, Chen ST, Lai MS. Increased risk of stroke associated with nonsteroidal anti-inflammatory drugs: a nationwide case-crossover study. Stroke 2010;41:1884-90.
23. Andersohn F, Schade R, Suissa S, Garbe E. Cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs and the risk of ischemic stroke: a nested case-control study. Stroke 2006;37:1725-30.
24. Bak S, Andersen M, Tsiropoulos I, Garcia Rodriguez LA, Hallsa J, Christensen K, et al. Risk of stroke associated with non-steroidal anti-inflammatory drugs. Stroke 2003;34:379-86.
25. Chou R, McDonagh MS, Nakamoto E, Griffin J. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. Comparative Effectiveness Review No. 38. (Prepared by the Oregon Evidence-based Practice Center under Contract No. HHSA 290 2007 10057 I) AHRQ Publication No. 11(12)-EHC076-EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
26. Binning A. Nimesulide in the treatment of postoperative pain: a double-blind, comparative study in patients undergoing arthroscopic knee surgery. Clin J Pain. 2007;23:565-70.
27. Pohjolainen T, Jekunen A, Autio L, Vuorela H. Treatment of acute low back pain with the COX-2-selective antiinflammatory drug nimesulide: results of a randomized, double-blind comparative trial versus ibuprofen. Spine 2000;25(12):1579-85.
28. Bellamy N, Buchanan WW, Grace E. Double-blind randomized controlled trial of isoxicam vs piroxicam in elderly patients with osteoarthritis of the hip and knee. Br J Clin Pharmacol 1986;22(Suppl 2):149S-155S.
29. Bartolucci P, El Murr T, Roudot-Thoraval F, Habibi A, Santin A, Renaud B, et al. A randomized, controlled clinical trial of ketoprofen for sickle-cell disease vaso-occlusive crises in adults. Blood 2009;114(18):3742-7.

30. Beltran J, Martin-Mola E, Figueroa M, Granados J, Sanmarti R, Artigas R, et al. Comparison of dexketoprofen trometamol and ketoprofen in the treatment of osteoarthritis of the knee. J Clin Pharmacol 1998;38:74S/
31. Boonriong T, Tangtrakulwanich B, Glabglay P, Nimmaanrat S: Comparing etoricoxib and celecoxib for preemptive analgesia for acute postoperative pain in patients undergoing arthroscopic anterior cruciate ligament reconstruction: a randomized controlled trial. BMC Musculoskel Dis 2010;11:246-50.
32. Daniels SE, Bandy DP, Christensen SE, Boice J, Losada MC, Liu H, et al. Evaluation of the dose range of etoricoxib in an acute pain setting using the postoperative dental pain model. Clin J Pain 2011;27:1-8.
33. Yilmaz H, Gurel S, Ozdemir O. The use and safety profile of non-steroidal antiinflammatory drugs among Turkish patients with osteoarthritis. Turk J Gastroenterol 2005;16(3):138-42.
34. Dougados M, Béhier J-M, Jolchine I, Calin A, van der Heijde D, Olivieri I, et al. Efficacy of celecoxib, a cyclooxygenase 2–specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal antiinflammatory drug. Arthritis Rheum 2001;44:180-5.
35. Ejstrup L, Knudsen JV, Petersen L. A randomised double-blind multicentre trial comparing tenoxicam and ketoprofen in osteoarthritis. Scand J Rheumatol Suppl 1989;80:48-53.
36. Comfort MB, Tse ASK, Tsang ACC, Mcgrath C. A study of the comparative efficacy of three common analgesics in the control of pain after third molar surgery under local anaesthesia. Aust Dent J 2002;47(4):327-30.
37. Porto A, Reis C, Perdigoto R, Gonçalves M, Freitas P, Macciocchi A. Gastroduodenal tolerability of nimesulide and diclofenac in patients with osteoarthritis. Current Therapeutic Research, Clinical & Experimental 1998;59(9):654-665.
38. Geba GP, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee. JAMA 2002;287:64-71.
39. Glina S, Damiao R, Afif-Abdo J, Santa Maria CF, Novoa R, Cairoli CE, et al. Efficacy and Safety of Parecoxib in the Treatment of Acute Renal Colic: A Randomized Clinical Trial. Int Braz J Urol 2011;37(6):697-705.
40. Pérez Gutthann S, García Rodríguez LA, Duque-Oliart A, Varas-Lorenzo C. Low-dose diclofenac, naproxen, and ibuprofen cohort study. Pharmacotherapy 1999;19:854-9.
41. Hawkey C, Kahan A, Steinbrück K, Alegre C, Baumelou E, Bégaud B, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. Br J Rheumatol 1998;37:937-45.
42. Hosie J, Distel M, Bluhmki E. Meloxicam in osteoarthritis: a 6-month, double-blind comparison with diclofenac sodium. Br J Rheumatol 1996;35(suppl. l):39-43.
43. Boardman PL, Hart FD. Side-effects of indomethacin. Ann Rheum Dis 1967;26(2):127-32.
44. Tarkkila P, Saarnivaara L. Ketoprofen, diclofenac or ketorolac for pain after tonsillectomy in adults? Br J Anaesth 1999;82(1):56-60.
45. Kokki H, Tuomilehto H, Tuovinen K. Pain management after adenoidectomy with ketoprofen: comparison of rectal and intravenous routes. Br J Anaesth 2000;85(6):836-40.
46. Kim JT, Sherman O, Cuff G, Leibovits A, Wajda M, Bekker AY. A double- blind prospective comparison of rofecoxib vs ketorolac in reducing postoperative pain after arthroscopic knee surgery. J Clin Anesth 2005;17:439-43.
47. Lanas A, García-Rodríguez LA, Arroyo MT, Gomollón F, Feu F, González-Pérez A, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut. Dec 2006;55(12):1731-8.
48. Lohmander LS, McKeith D, Svensson O, Malmenäs M, Bolin L, Kalla A, et al. A randomised, placebo controlled, comparative trial of the gastrointestinal safety and efficacy of AZD3582 versus naproxen in osteoarthritis. Ann Rheum Dis 2005;64(3):449-56.
49. Merry AF, Webster CS, Holland RL, Middleton NG, Schug SA, James M, et al. Clinical tolerability of perioperative tenoxicam in 1001 patients-a prospective, controlled, double-blind, multi-centre study. Pain 2004;111(3):313-22.

50. Miceli-Richard C, Le Bars M, Schmidely N, Dougados M. Paracetamol in osteoarthritis of the knee. Ann Rheum Dis 2004;63(8):923-30.
51. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000;343:1520-8.
52. Pincus T, Koch G, Lei H, Mangal B, Sokka T, Moskowitz R, et al. Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. Ann Rheum Dis 2004;63(8):931-9.
53. Rahme E, Nedjar H. Risks and benefits of COX-2 inhibitors vs non-selective NSAIDs: does their cardiovascular risk exceed their gastrointestinal benefit? A retrospective cohort study. Rheumatology 2007;46(3):435-438.
54. García Rodríguez LA, Cattaruzzi C, Troncon MG, Agostinis L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal antiinflammatory drugs, calcium antagonists, and other antihypertensive drugs. Arch Intern Med 1998;158:33-9.
55. Scott DL, Berry H, Capell H, Coppock J, Daymond T, Doyle DV, et al. The long-term effects of non-steroidal anti-inflammatory drugs in osteoarthritis of the knee: a randomized placebo-controlled trial. Rheumatology 2000;39(10):1095-101.
56. Singla N, Singla S, Minkowitz HS, Moodie J, Brown C. Intranasal ketorolac for acute postoperative pain. Curr Med Res Opin 2010;26(8):1915-23.
57. Strom BL, Berlin JA, Kinman JL, Spitz PW, Hennessy S, Feldman H, et al. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding: a postmarketing surveillance study. JAMA 1996;275:376-382.
58. Distel M, Mueller C, Bluhmki E, Fries J. Safety of meloxicam: a global analysis of clinical trials. Br J Rheumatol 1996;35(Suppl 1):68-77.
59. Singh G, Fort JG, Goldstein JL, Levy RA, Hanrahan PS, Bello AE, et al. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. Am J Med 2006;119:255-66.
60. Tannenbaum H, Berenbaum F, Reginster J, Zacher J, Robinson J, Poor G, et al. Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a 13 week, randomised, double blind study versus placebo and celecoxib. Ann Rheum Dis 2004;63:1419-26.
61. Daniels SE, Torri S, Desjardins P. Valdecoxib for treatment of primary dysmenorrhea. J Gen Intern Med 2005;20(1):62-7.
62. Yocum D, Fleischmann R, Dalgin P, Caldwell J, Hall D, Roszko P. Safety and efficacy of meloxicam in the treatment of osteoarthritis. Arch Intern Med 2000;160:2947-54.
63. Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. Lancet 2004;364(9435):665-74.
64. Brogden RN, Speight TM, Avery GS. Ketoprofen: a preliminary report of its pharmacological activity and therapeutic efficacy in rheumatic disorders. Drugs 1974;8:168-75.
65. Moore RA, Derry S, McQuay HJ. Discontinuation rates in clinical trials in musculoskeletal pain: meta-analysis from etoricoxib clinical trial reports. Arthritis Res Ther 2008;10:R53 (doi:10.1186/ar2422)
66. Zhang JJ, Ding E, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: a class-wide meta-analysis. JAMA 2006; 296(13):1619-32.
67. Fries JF. NSAID gastropathy: the second most deadly rheumatic disease? Epidemiology and risk appraisal. J Rheumatol 1991;18(Suppl 28):6-10.
68. Luton K, Garcia C, Poletti E, Koester G. Nicolau Syndrome: three cases and review. Int J Dermatol 2006;45(11):1326-8.
69. Menniti-Ippolito F, Maggini M, Raschetti R, Da Cas R, Traversa G, Walker AM Ketorolac use in outpatients and gastrointestinal hospitalization: a comparison with other non-steroidal anti-inflammatory drugs in Italy. Eur J Clin Pharmacol 1998;54:393-7.