

# Systematic Review: Is There Contraindication to the Concomitant Use of Non-Steroidal Anti-Inflammatory Drugs and Steroids?

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**Objectives:** To analyze the safety of combining non-steroidal anti-inflammatory drugs (NSAID) and steroids.

**Methods:** A systematic review following a sensitive search strategy was performed. All articles published in MEDLINE (since 1961), EMBASE (since 1961), and Cochrane Library, up to December 2007 were examined. Selection criteria: the population (subjects with musculoskeletal diseases on steroids), the intervention (concomitant use of NSAID), and outcomes related to drugs safety (gastrointestinal, renal, and cardiovascular toxicity). Titles and abstracts of retrieved articles meeting inclusion criteria from the search were reviewed. Only randomized controlled trials (RCT) or high quality cohort studies with a control group were included.

**Results:** Of a total of 4164 references retrieved, 42 were analyzed in detail, and 10 were finally included, 6 RCT and 4 prospective cohort studies, which included more than 20 000 patients.

**Conclusions:** The use of NSAID and low dose of steroids in patients with musculoskeletal diseases does not seem to increase the risk of gastrointestinal adverse events.

**Key words:** Non-steroidal anti-inflammatory drugs. Steroids. Safety.

**Métodos:** Revisión sistemática. Se definió una estrategia de búsqueda bibliográfica sensible en MEDLINE (desde 1961), EMBASE (desde 1980) y Cochrane Library hasta diciembre del 2007, definiendo la población (sujetos con enfermedad reumática en tratamiento con esteroides) y la intervención (tratamiento concomitante con AINE) y definiendo como resultados variables de seguridad (toxicidad gastrointestinal, renal y cardiovascular). Se seleccionaron ensayos clínicos y estudios de cohortes de calidad.

**Resultados:** Se recuperaron 4.164 estudios, de los que 42 se analizaron en detalle; finalmente se incluyeron 10 en los análisis, 6 de los cuales fueron ensayos clínicos y 4, estudios de cohortes prospectivos, que incluyeron a más de 20.000 pacientes.

**Conclusiones:** El uso concomitante de AINE y esteroides a dosis bajas en pacientes con enfermedad reumática no parece que incremente el riesgo de eventos adversos gastrointestinales.

**Palabras clave:** Antiinflamatorios no esteroideos. Esteroides. Seguridad.

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## Revisión sistemática: ¿hay alguna razón para contraindicar el uso concomitante de antiinflamatorios no esteroideos y esteroides?

**Objetivos:** Analizar la seguridad del uso concomitante de antiinflamatorios no esteroideos (AINE) con esteroides en pacientes con enfermedad reumática.

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## Introduction

The use of non-steroidal anti-inflammatory drugs (NSAID) is very frequent in the population with rheumatic disease.

The relationship of NSAID with gastroduodenal complications (ulcer, hemorrhage, perforation),<sup>1</sup> although independent risk factors have also been identified associated to these digestive complications in NSAID consumers, such as advanced age, a history of gastroduodenal ulcer, alcohol consumption, or the use of antiplatelet or anticoagulant medication.<sup>2</sup>

On the other hand, the gastroerosive effect of other drugs, such as steroids, have also been studied, although in this case their risk is controversial; according to some publications, oral steroids would double the risk of gastrointestinal complications, an effect which, in addition, depend on the dose.<sup>3</sup> Because current use of steroids and

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NSAID by the specialty of rheumatology is very frequent for the treatment of rheumatic diseases, determining the possible effects (especially in relation to the gastrointestinal toxicity, although extensible to any other adverse event) is of a lot of importance in our medium.

Because all of the above, the objective of this systematic review is to search for published evidence regarding the safety of the concomitant use of NSAID and steroids, therefore contributing for a better management of our patients.

## Material and Methods

A systematic review was carried out to analyze the safety of the concomitant use of NSAID and steroids. The selection criteria of the studies were: *a)* studies in which the patients has a diagnosis of some musculoskeletal disease and where under steroid treatment, without a restriction regarding the dose and dose of the drug; *b)* studies in which the patients, apart from steroid, concomitantly took some NSAID, without restriction regarding the type and dose, but excluding studies in which the subjects took NSAIDs at an antiplatelet drugs and not at a non-analgesic/anti-inflammatory dose or topical treatment; *c)* to evaluate the safety of the concomitant use of the drugs, including studies which analyzed one of the following variables: gastrointestinal (such as bleeding, perforation, obstruction, etc), renal and cardiovascular toxicity, among others; and *d)* clinical

trials (CT) and cohort studies (prospective or retrospective) with good quality. Studies which only provided pharmacokinetic and/or pharmacodynamic data, as well as studies in healthy volunteers and animals were also excluded. Finally, articles both in English and Spanish were selected.

The following electronic databases were searched up until December 2007: MEDLINE (since 1960), EMBASE (since 1980), and Cochrane Library (Central). Both MeSH and free text formats were searched. No limits were set on the publication date. The specific search strategy is detailed in Tables 1 and 2. No manual search was done of publications from national (SER) or international (ACR, EULAR) meetings, because of the great volume of articles recovered from the electronic databases.

A single reviewer analyzed the articles which resulted from the search strategy, as well as the detailed analysis of the included articles. The result of the search was primarily thinned out by title and abstract, or by the complete article in case no abstract was available, through 20 min sessions maximum duration. After this process, the remaining articles were analyzed in detailed. Finally, a manual search with the references of the selected articles for their detailed analysis. All of the references were recovered from the internet and introduced into the Procite 5.1 software for ease of management.

In order to evaluate the methodological quality of the included studies the Jadad<sup>4</sup> score was used for the CT (1 to 5, considering good quality studies with Jadad 3-5) and, for the cohort studies, the Oxford quality score.

**TABLE 1. Search Strategy and Articles Recovered From MEDLINE**

#	Search Strategy	Results
1	(Steroids OR steroid OR corticoids OR corticoid OR corticosteroids OR corticosteroid OR glucosteroids OR glucosteroid OR glucocorticoids OR glucocorticoid OR prednisone OR prednison OR prednisolone OR methylprednisolone OR cortisone OR cortisol OR triamcinolone OR dexamethasone OR betamethasone)	738 575
2	NSAID OR Nonsteroidal Anti-Inflammatory Agents OR Nonsteroidal Antiinflammatory Agents OR Analgesics, Anti Inflammatory OR Non-Steroidal Anti-Rheumatic Agents OR Non-Steroidal Antirheumatic Agents OR Aspirin-Like Agents OR Agents, Aspirin-Like OR naproxen* OR ibuprofen* OR dexibuprofen OR dexketoprofen OR flurbiprofen OR Ketoprofen OR Ketorola* OR aceclofenac OR diclofenac OR lornoxicam OR meloxicam OR piroxicam OR tenoxicam OR indometacin OR sulindac OR tolmetin OR fenilbutazon OR Phenylbutazone OR nabumeton OR celecoxib OR etoricoxib OR parecoxib OR rofecoxib OR valdecoxib OR lumiracoxib OR salicylic acid OR acetylsalicylic acid OR diflunisal OR Cyclooxygenase 2 Inhibitors OR COX-2 Inhibitors OR COX2 Inhibitors, OR Coxibs	150 391
3	Randomized [All Fields] OR random allocation"[TIAB] NOT Medline[SB]) OR "random allocation"[MeSH Terms] OR randomized [Text Word] OR controlled[All Fields] AND ("clinical trials as topic"[MeSH Terms] OR trial[Text Word]) OR placebo OR blinded	819 404
4	#1 AND #2 AND #3	2430
5	acute [All Fields] OR acute OR post-operative [All Fields] OR post-surgical[All Fields] OR postsurgical [All Fields] OR postoperative [All Fields] OR postoperative OR Postoperative Complications [Mesh] OR intraoperative [All fields] OR Intraoperative Complications [Mesh] dysmenorrhoea [All Fields] OR dysmenorrhea OR orthodontic [All fields]	28 328
6	#4 NOT #5	2411
7	#6 LimitsLimits: Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, English, Spanish	1243

**TABLE 2. Search Strategy and Articles Recovered From EMBASE**

#	Search Strategy	Results
1	steroids.mp. or exp Steroid / OR glucocorticoids.mp. or exp Glucocorticoid /	568 743
2	nsaid.mp. or Nonsteroid Antiinflammatory Agent/ or Nonsteroidal Anti-Inflammatory Agents.mp. or (coxib or Cyclooxygenase 2 Inhibitor).mp. or Acetylsalicylic Acid/ or Aspirin-Like Agents.mp. or naproxen.mp. or NAPROXEN/ or ibuprofen.mp. or IBUPROFEN/ or dexibuprofen\$.mp. or DEXIBUPROFEN/ or dexketoprofen.mp. or DEXKETOPROFEN/ or flurbiprofen.mp. or FLURBIPROFEN/ or Ketoprofen.mp. or KETOPROFEN/ or KETOROLAC/ or Ketorolac.mp. or aceclofenac.mp. or ACECLOFENAC/ or diclofenac.mp. or DICLOFENAC/ or lornoxicam.mp. or LORNOXICAM/ or meloxicam.mp. or MELOXICAM/ or PIROXICAM/ or piroxicam.mp. or PIROXICAM/ or piroxicam.mp. or tenoxicam.mp. or TENOXICAM/ or INDOMETACIN/ or indometacin.mp. or sulindac.mp. or SULINDAC/ or tolmetin.mp. or TOLMETIN/ or Phenylbutazone.mp. or PHENYLBUTAZONE/ or nabumetone/ or nabumeton.mp. or celecoxib.mp. or CELECOXIB/ or etoricoxib.mp. or ETORICOXIB/ or parecoxib.mp. or PARECOXIB/ or rofecoxib.mp. or ROFECOXIB/ or salicylic acid.mp. or Salicylic Acid/ or acetylsalicylic acid.mp. or Acetylsalicylic Acid/ or diflunisal.mp. or DIFLUNISAL/ or valdecoxib.mp. or VALDECOXIB/ or lumiracoxib.mp. or LUMIRACOXIB/	207 945
3	exp clinical trial/ or evidence based medicine/ or outcomes research/ or crossover procedure/ or double blind procedure/ or single blind procedure/ or prospective study/ or major clinical study/ or exp comparative study/ or placebo/ or "evaluation and follow up"/ or follow up/ or randomization/	1 964 112
4	controlled study/ not case control study/	2 568 695
5	3 or 4	3 774 593
6	((clinic\$ adj5 trial\$) or ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)) or random\$ or placebo\$.ti,ab.	489 355
7	5 or 6	3 890 101
8	1 and 2 and 7	17 876
9	perioperative period.mp. or PERIOPERATIVE PERIOD/ or perioperative care.mp. or SURGERY/ or surgery.mp. or SURGICAL TECHNIQUE/ or surgical procedures.mp. or PEROPERATIVE CARE/ or preoperative care.mp. or intraoperative care.mp. or PEROPERATIVE COMPLICATION/ or POSTOPERATIVE COMPLICATION/ or dysmenorrhoea.mp. or Dysmenorrhea/ or orthodontic.mp. or Orthodontics/ or exp malignant neoplastic disease/ or cancer/ or exp metastasis/ or exp mixed tumor/ or exp "neoplasms of uncertain behavior"/ or exp neoplasms subdivided by anatomical site/ or exp "oncogenesis and malignant transformation"/ or exp paraneoplastic syndrome/ or exp "precancer and cancer-in-situ"/ or adolescent.mp. or adolescent/ or hospitalized adolescent/ or juvenile.mp. or juvenile/ or child.mp. or child/ or boy.mp. or boy/ or gifted child/ or girl.mp. or girl/ or handicapped child/ or hospitalized child/ or preschool child/or school child/ or infant.mp. or infant/ or baby.mp. or baby/ or high risk infant/ or hospitalized infant/ or newborn.mp. or newborn/ or suckling.mp. or suckling/ or pediatric.mp. or review/ or guideline.mp.	3 370 213
10	8 not 9	666 390
11	exp musculoskeletal disease/ or musculoskeletal disease.mp. or rheumatic polymyalgia.mp. or polymyalgia/ or lupus erythematosus systemic.mp. or systemic lupus erythematosus/ or vasculitis/ or vasculitis.mp. or polymyositis.mp. or polymyositis/ or dermatomyositis.mp. or dermatomyositis/	
12	10 and 11	3391
13	Limit 12 to humans, abstracts	2091

## Results

The results of the search is detailed in Figure. In the end, 10 articles were included. A total of 6 were CT<sup>5-10</sup> and 4, studies of prospective cohort<sup>11-14</sup> which included more than 20 000 patients.

## Summary of the Evidence

The description of the main results of the included studies are shown as follows, which can be consulted in Table 3. The list of the excluded articles<sup>15-47</sup> and the cause for exclusion from the systematic review are detailed on Table 4.

As has been commented, 10 articles with good quality were included, 6 CT (Jadad 3) and 4 prospective cohort studies (quality 2a). This studies analyze patients with rheumatoid arthritis (RA) and/or osteoarthritis (OA), most of them middle aged women. The duration of treatment varied from 1 to 15 weeks in CT and 3-21 years in cohorts, or this data was unavailable. Different types of NSAID and steroids were employed, as well as doses, although the most commonly employed steroid was prednisone at a low dose, close to 10 mg/day. Most of the studies did not expressly permit the use of gastric protectors or did not register patients taking them. With relation to safety, not enough evidence to contraindicate the concomitant use of steroids and

**TABLE 3. Included Studies, Characteristics, and Main Results<sup>a</sup>**

Study	Participants and Intervention	Results
Benito-Garcia <sup>11</sup> ; prospective cohort; 3 year follow-up; quality, 2a	n= 4240 RA/OA (79% women; mean age, 61); COX2 + prednisone (n=1314)	RR (adjusted) not significant for: epigastric discomfort (P=.8), gastric acidity (P=.88), nausea (.066), gastroduodenal ulcer (P=.259)
Fries <sup>12</sup> ; prospective cohort; 4 year follow-up; quality 2a	n=2224 RA; NSAID: naproxen, acetyl salicylic acid, piroxicam, sulindac, ibuprophen + prednisone (mean dose, 7 mg/day)	Rate of hospitalization due to gastrointestinal event: NSAID versus NSAID + prednisone (0.86% vs 1.59%; P>.050); naproxen versus naproxen + prednisone (1.14% vs 2.58%; P>.50); ASA versus ASA + prednisone (1.26% vs 2.22%; P>.050); piroxicam versus piroxicam + prednisone (2.22% vs 1.79%; P>.050); sulindac versus sulindac + prednisone (2.1% vs 0.75%; P>.050); ibuprophen versus ibuprophen + prednisone (0.89% vs 7.8%; P>.050)
Gabriel <sup>13</sup> ; prospective cohort; 21 year follow-up; quality 2a	n=232 PMR (70% women; mean age, 72 years). EC: RA, SLE, PM, infections, myeloma. NSAID + steroids (n=51); NSAID alone (n=57); steroids alone (n=124); mean duration of treatment, 2.5 years	a) Any adverse event: NSAID alone (n=38), NSAID + steroids (n=41) (P=.120); b) gastroduodenal hemorrhage: NSAID alone (n=5), NSAID + steroids (n=2) (P>.050)
Goldstein <sup>5</sup> ; CT double blind, multicentric; 12 weeks follow up; Jadad 3	n=536 RA/OA (67% women; mean age, 57 years); EC: other inflammatory diseases, active gastrointestinal disease, gastric protectors, NSAID; celecoxib 400 mg/day 12 weeks (n=185); celecoxib 400 mg/day + steroids 12 weeks (n=26); naproxen 1000 mg/day 12 weeks (n=194); naproxen 1000 mg/day + steroids 12 weeks (n=20)	Gastroduodenal ulcer (endoscopic diagnosis); celecoxib (n=16); celecoxib + steroids (n=2) (P=.969); naproxen (n=79); naproxen + steroids (n=8) (P>.050)
Jick <sup>6</sup> ; crossed CT; 2 week follow-up; Jadad 3	n=26 patients with rheumatic disease (75% women; mean age, 54 years): dexamethasone 1.5 mg/day 1 week (n=26); dexamethasone 0.75 mg/day 1 week + ASA 1500 mg/day 1 week (n=26)	a) Gastrointestinal alterations (pain, nausea, diarrhea); dexamethasone (n=3), dexamethasone + AAS (n=0) (P=.074); b) alterations in CNS (headache, vertigo, tinnitus): dexamethasone (n=2), dexamethasone + ASA (n=5) (P=.222); c) chest pain: dexamethasone (n=0), dexamethasone + ASA (n=1) (P=.312)
Laine <sup>7</sup> ; CT multicentric blind; 13 month follow up; Jadad 3	n=8076 RA (79.7% women; mean age, 58 years). EC: gastric protectors. Rofecoxib 50 mg/day (n=4047); naproxen 1000 mg/day (n=4029); tall taking steroids	Incidence (100 patients-year) of gastrointestinal trastorn (bleeding, perforation obstruction, ulcus): rofecoxib only, 2.1; rofecoxib + steroids, 2.1 (P=1); naproxeno only, 4.5; naproxeno + steroids, 5.67 (P=.274)
Laine <sup>8</sup> ; CT multicentric blind; 13 month follow-up; Jadad 3	n=8076 RA (79.7% women; mean age, 58 years). EC: gastric protectors. Rofecoxib 50 mg/day + steroids (n=4047); naproxen 1000 mg/day + steroids (n=4029)	Relative risk for bleeding, perforation, obstruction, ulceration, diverticulitis, large intestine: rofecoxib, RR=0.26; rofecoxib + steroids, RR=0.59 (P>.050); naproxen, RR=0.99; naproxen + steroids, RR=0.76 (P>.050)
Littman <sup>9</sup> ; CT double blind placebo control; 15 weeks follow up; Jadad 3	n=32 PMR (63% women; mean age, 66). EC: other rheumatic diseases. Tenidap 120 mg/day + prednisone <10 mg/day 15 weeks (n=16); placebo + steroids <10 mg/day 15 weeks (n=16)	a) Gastroduodenal ulcer: tenidap + steroids (n=1), steroids (n=0) (P=.242); b) increase in transaminases: tenidap + steroids (n=3), steroids (n=0) (P=.045)
Paulus <sup>10</sup> ; CT; 3 year follow-up; Jadad 3	n=1434 RA (71% women; mean age, 52 years). EC: other NSAID or DMARD, prednisone >5 mg/day. NSAID: etodolac 300 mg/day, etodolac 1000 mg/day or ibuprophen 2400 mg/day (n=1105); NSAID (prior) + prednisone <5 mg/day (n=328)	a) Any adverse event: NSAID (n=118), NSAID + prednisone n=34) (P=.439); b) alterations in the laboratory analysis: (AINE (n=30), AINE + prednisone (n=7) (P=.212)
Wolfe <sup>14</sup> ; prospective cohort; 13 year follow-up; quality 2a	n=8605 RA/OA. NSAID; NSAID + prednisone	Incidence of hospitalization in RA (100 patients/year) due to gastrointestinal bleeding: prednisone, 0.97 (0.43-2.14); NSAID, 0.19 (0.09-0.39); NSAID + prednisone, 1.31 (0.82-2.08)

<sup>a</sup>CT indicates clinical trials; DMARD, disease modifying drugs; EC, exclusion criteria; NSAID, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; PM, polymyositis; PMR, polymyalgia rheumatica; RR, relative risk; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

**TABLE 4. Excluded Studies (by Author and Date of Study) and Motives for Exclusion<sup>a</sup>**

Study	Motive for Exclusion
Abelson <sup>16</sup> (1989)	Steroids. No rheumatic disease
Ambanelli <sup>17</sup> (1991)	Steroids. No specific data on the concomitant use of steroids and NSAID
Avidan <sup>18</sup> (2001)	Steroids. No specific data on the concomitant use of steroids and NSAID
Awni <sup>19</sup> (1995)	Steroids. Healthy volunteer. No specific data on the concomitant use of steroids and NSAID
Badia <sup>20</sup> (1975)	Steroids. No specific data on the concomitant use of steroids and NSAID
Bowers <sup>21</sup> (1975)	Steroids. No specific data on the concomitant use of steroids and NSAID
del Campo <sup>22</sup> (1981)	Steroids. Not able to correctly evaluate concomitant use of steroids and NSAID
Flores <sup>23</sup> (1973)	Steroids. Not able to correctly evaluate concomitant use of steroids and NSAID
Furtado <sup>24</sup> (2005)	Steroids. No specific data on the concomitant use of steroids and NSAID
Garcia <sup>25</sup> (2006)	Steroids. No relation to the research question
Garg <sup>26</sup> (1992)	Steroids. Healthy volunteers. No specific data on the concomitant use of steroids and NSAID
Gergely <sup>27</sup> (1989)	Steroids. No specific data on the concomitant use of steroids and NSAID
Goycochea-Robles <sup>28</sup> (2007)	Steroids. No relation to the research question
Green <sup>29</sup> (1998)	Steroids. No branch that studies concomitant use of steroids and NSAID
Harris <sup>30</sup> (2006)	Steroids. No relation to the research question
Helin-Salmivaara <sup>31</sup> (2005)	Steroids. No relation to the research question
Hochain <sup>32</sup> (1995)	Steroids. Poor quality
Hernández-Díaz <sup>15</sup> (2001)	Steroids. General population study
Holvoet <sup>33</sup> (1991)	Steroids. No relation to the research question
Huerta <sup>34</sup> (2005)	Steroids. No specific data on the concomitant use of steroids and NSAID
Joshi <sup>35</sup> (1977)	Steroids. No specific data on the concomitant use of steroids and NSAID
Kolopp-Sarda <sup>36</sup> (2001)	Steroids. No relation to the research question
Komajda <sup>37</sup> (2003)	Steroids. No relation to the research question
Lanier <sup>38</sup> (1987)	Steroids. No specific data on the concomitant use of steroids and NSAID
Luftschein <sup>39</sup> (1979)	Steroids. No specific data on the concomitant use of steroids and NSAID
Martinez <sup>40</sup> (1988)	Steroids. No specific data on the concomitant use of steroids and NSAID
Martio <sup>41</sup> (1980)	Steroids. No specific data on the concomitant use of steroids and NSAID
McNeil <sup>42</sup> (1993)	Steroids. No specific data on the concomitant use of steroids and NSAID
Neustadt <sup>43</sup> (1987)	Steroids. No specific data on the concomitant use of steroids and NSAID
Paulus <sup>44</sup> (2004)	Steroids. No relation to the research question
Rejholec <sup>45</sup> (1979)	Steroids. No specific data on the concomitant use of steroids and NSAID
Sheldon <sup>46</sup> (2003)	Steroids. No specific data on the concomitant use of steroids and NSAID
Tougas <sup>47</sup> (1987)	Steroids. Opinion article

<sup>a</sup>NSAID indicates non-steroidal anti-inflammatory drugs.

NSAID in patients with rheumatic disease was found. This is based on the lack of a clear relationship between the combined use of these drugs and the appearance of

adverse gastrointestinal events (mild or severe) or other types of events, in comparison of NSAID without steroids.

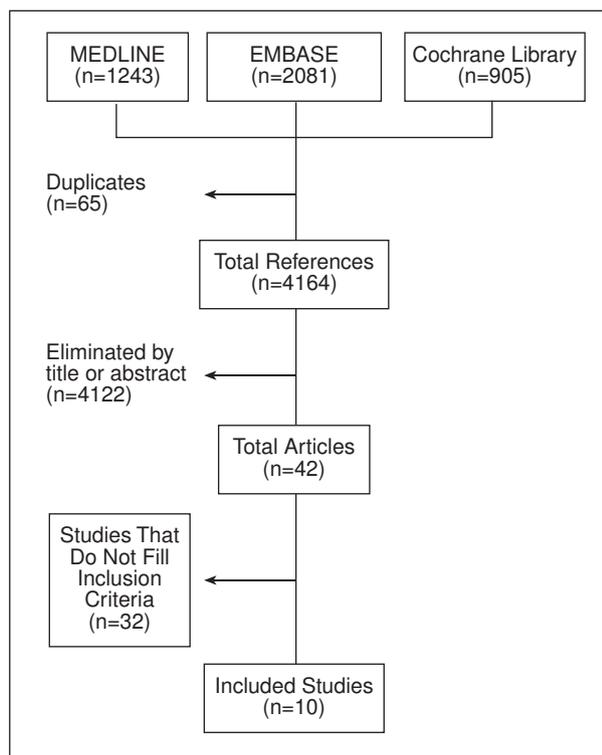


Figure. Flow of study selection.

### Detailed Results of the Combined Use of NSAID and Steroids

Among the CT safety results of the combined use of NSAID and steroids, the following merit mentioning:

- In the study by Goldstein et al,<sup>5</sup> it was seen that the use of celecoxib 400 mg/day or naproxen 1000 mg/day with steroids for 12 weeks was not associated to gastroduodenal ulcer in comparison with these NSAID without steroids
- According to Jick et al,<sup>6</sup> the use of acetyl salicylic acid 1500 mg/day with dexamethasone 0.75 mg/day during 1 week, in comparisons with dexamethasone alone, was not associated to a larger number of minor gastrointestinal developments (not included ulcer or hemorrhages), CNS problems (headache, vertigo, tinnitus), or chest pain
- In the articles by Laine et al,<sup>7,8</sup> it was seen that the use of rofecoxib 50 mg/day or naproxen 1000 mg/day with steroids, in comparison to the use of NSAID alone, was not associated to a larger risk of upper and lower severe adverse digestive events (ulcer, hemorrhage, perforation, obstruction, or diverticulitis)
- In the article by Littman et al,<sup>9</sup> the use of tenidap 120 mg/day plus prednisone (<10 mg/day) during 15 weeks,

in comparison to NSAID in monotherapy, was not associated to a larger risk of gastroduodenal ulcer, but it was associated to a larger number of analytic alterations – In the study by Paulus et al,<sup>10</sup> the use of NSAID (etodolac 300 mg/day, etodolac 1000 mg/day, or ibuprofen 2400 mg/day) with prednisone (<5 mg/day), in comparison with NSAID alone, was not associated with the appearance of a larger number of adverse events or laboratory alterations

As for the prospective cohort studies, 4 were included: Benito-García et al,<sup>11</sup> Fries et al,<sup>12</sup> Gabriel et al,<sup>13</sup> and Wolfe et al.<sup>14</sup> They analyzed a total of 12 365 patients. In general, the incidence of a serious gastrointestinal events was low and not associated to the concomitant use of NSAID and steroids. The study of Wolf et al,<sup>14</sup> showed that the combination of NSAID and steroids did not increase the risk of an important gastrointestinal event in comparison with NSAID monotherapy, while steroid monotherapy led to an increase in the risk for the event.

### Discussion

The safety of the concomitant use of steroids and NSAIDs in patients has been analyzed in the present systematic review. To that end, an extensive search of the main bibliographic databases available was performed, as has been described above. The only studies included were CT and quality cohorts, considering that it was the best way to answer this research question.

Finally, 10 studies were included (6 CT,<sup>5-10</sup> 4 cohort studies<sup>11-14</sup>) of acceptable quality: the CT were all Jadad 3 and the cohorts, quality 2a. Regarding the patients studied, all had some sort of musculoskeletal condition, although it is important to mention that practically all suffered from osteoarthritis or rheumatoid arthritis. NSAID and steroids studies were diverse, as were the prescribed doses (in those studies in which this data was available). In relation to the events studied, all of the included articles evaluated gastrointestinal adverse events, and most of them also analyzed the most relevant and/or severe clinically relevant adverse events, such as gastroduodenal ulcer or digestive tract hemorrhage. In general, these outcome measures were defined by very similar criteria in all of the studies.

First, in the present systematic review, it has been seen that the general incidence of severe gastrointestinal adverse events (bleeding, perforation, obstruction, etc) which could generate a hypothesis that contraindicated the combined use of both drugs, is low. In addition, the results of the CT indicate that the combination does not increase the risk of gastrointestinal adverse events (both severe and others such as mild dyspepsia or nausea) and others (central nervous system alterations or chest pain) in comparison with the use of NSAID without steroids. Regarding the

cohort studies, the fact that the combines use of NSAID and steroids increased the risk of a gastrointestinal adverse event in comparison to its use as monotherapy was not demonstrated either. Among them, the study by Wolfe et al<sup>16</sup> stands out, in which the combination of NSAID and steroids did not increase the risk of a severe gastrointestinal event related to steroids, which were the ones with an increased incidence. Due to this, the use of NSAID in combination with steroids can be recommended (at least at a low dose), in patients with musculoskeletal disease, with a 2a evidence and a B/C recommendation strength.

However, this data must all be interpreted very cautiously, because they are not exempt of some limitations. In the case of the CT, limitations are derived over all due to the representativity of the patients included in them, because they are probably not like other patients which usually are followed by rheumatology consults, in other words, patients with a greater deal of independent risk factors for gastrointestinal adverse events, such as advanced age, comorbidity, etc.

On the other hand, in cohort studies it is very difficult to clearly define the duration and dose of the studied drugs to be able to establish more solid causal relationships between the pharmacologic combinations and their possible side effects.

But, from another perspective, it is important to comment that this data contrasts with publications dealing with the general population and the use of NSAID and steroids, in which an increased risk of severe gastrointestinal complications has been described.<sup>28</sup> This could be due, in part at least, to—as has been described clearly in 2 of the CT and 1 of the cohort studies, and probably happens in the rest—the steroid doses used for the studies included in this review tended to be low, lower even than those taken by many patients with rheumatic disease. In general, they are much lower steroid doses than those used, for example, for the treatment of other affections such as lung and some neurological ones, which would be included in the population studies, probably increasing the risk of an adverse event related to the concomitant use of NSAID and steroids.

Continuing with the adverse events in relation with these drugs, there is no doubt that the gastrointestinal ones, due to their frequency and potential severity, are obligately to be studied and followed, but it must pointed out that the lack of available information on other types of events which might be of interest, such as renal or cardiovascular. One last point, in relation to the combined use of NSAID and steroids, in this systematic review there were studies included with different drugs, both NSAID and steroids (although clearly the most used steroid was prednisone), as well as different doses and combinations of both, making it extremely difficult to establish comparisons among them to establish which combination of NSAID and steroids (and at what dose each) represents a better safety profile.

For that, other specially designed studies will have to be performed in order to respond to that question.

In conclusion, the use of NSAID with steroids at a low dose in patients with musculoskeletal affection does not seem to increase the risk of both mild and severe gastrointestinal adverse events, making it possible to recommend their use in daily practice.

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