Systematic Review: Is the Use of NSAIDs Effective and Safe in the Elderly?

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Objective: To analyze the efficacy and safety of non-steroidal anti-inflammatory drugs (NSAID) in the elderly.
Methods: We performed a systematic review using a sensitive search strategy. All studies published in MEDLINE (since 1961), EMBASE (since 1961), and Cochrane Library (up to December 2007) were selected. We defined the population (elderly as subjects aged 60 years or above with musculoskeletal diseases), the intervention (use of NSAID), and the results related to efficacy (pain, function, and quality of life) and safety (gastrointestinal, cardiovascular, or renal toxicity). Randomized clinical trials (RCT) (Jadad 4 or 5) and high quality cohort studies were included.
Results: A total of 101 studies were analyzed in detail, and 16 were included. More than 50 000 patients aged 60 years or above were analyzed from 1 week, up to 4 years. Different NSAID were included as well as different outcomes. Four meta-analyses, 9 RCT, 2 cohort studies, and 1 cross-sectional study were included. NSAID are effective for the treatment of musculoskeletal pain, stiffness or joint function. However, NSAID are associated with an increased risk of any serious adverse events, especially serious gastrointestinal adverse events (death, hospitalization, bleeding, ulcers, obstruction). This risk decreased with the use of proton pump inhibitors.
Conclusions: Based on the evidence, NSAID in the elderly are effective for the treatment of different musculoskeletal diseases, although the risk of serious adverse events (mainly gastrointestinal) is also clearly increased.

Key words: Non-steroidal anti-inflammatory drugs. Elderly. Efficacy. Safety.

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Revisión sistemática: ¿es eficaz y seguro el uso de AINE para los ancianos?

Objetivo: Analizar la eficacia y la seguridad de los antiinflamatorios no esteroideos (AINE) en ancianos.
Métodos: Revisión sistemática. Se definió una estrategia de búsqueda bibliográfica sensible en MEDLINE (desde 1961), EMBASE (desde 1980) y Cochrane Library (hasta diciembre de 2007); se definió la población (ancianos: sujetos mayores de 60 años, con enfermedades reumáticas), la intervención (AINE) y los resultados; variables de eficacia (dolor, función, calidad de vida) y de seguridad (toxicidad gastrointestinal, renal y cardiovascular). Se incluyeron ensayos clínicos (EC) de 4-5 en la escala de Jadad y estudios de cohortes de máxima calidad.
Resultados: Se seleccionaron 101 artículos para lectura en detalle, de los que se incluyeron 16, que analizaron más de 50.000 ancianos, con un seguimiento que varió desde 1 semana a 4 años. Destaca la gran diversidad en cuanto al tipo de AINE y las medidas de desenlace. Se incluyeron 4 metaanálisis, 9 EC, 2 estudios de cohortes y un estudio de prevalencia. La mayoría de estos estudios analizaron a pacientes con osteoartrosis o artritis reumatoide. Los AINE en el anciano se han mostrado eficaces para el control del dolor de origen reumático, la rigidez y la función articular, pero presentan un riesgo aumentado de cualquier evento grave, especialmente gastrointestinal (muerte, hospitalización, hemorragia, ulcus u obstrucción digestiva). Este riesgo disminuye al asociarse un protector gástrico.
Conclusiones: De acuerdo con la evidencia recogida, el uso de AINE es eficaz para el tratamiento de ancianos con enfermedades reumáticas, aunque también presenta un riesgo aumentado de evento adverso grave, sobre todo de origen gastrointestinal.

Palabras clave: Antiinflamatorios no esteroideos. Ancianos. Eficacia. Seguridad.

Introduction

The use of non-steroidal anti-inflammatory drugs (NSAID) is very frequent in patients with rheumatic

disease, especially in degenerative processes such as osteoarthritis and inflammatory disease such as rheumatoid arthritis.

According to general population studies, elderly patients seem to be more susceptible to developing adverse events related to the use of NSAID, especially in the digestive tract; in fact, some studies have manifested that elderly patients have 5 times more risk of gastrointestinal toxicity when using these drugs.[1-3] Multiple factors seem to be implicated in the development of NSAID-induced gastrointestinal toxicity in the elderly. Among these, direct damage to the digestive mucosa, the inhibition of protective endogenous prostaglandins, the increase in bleeding time and a possible reduction in the capacity to eliminate these drugs which could lead to an increase in blood concentrations of the drug are the most important.[4,5] But, in addition, and probably in relation to the inhibition of prostaglandins, NSAID-related renal alterations have been described in elderly patients, which could produce important changes in glomerular filtration and blood pressure and, in patients with ventricular disfunction, constitute a risk factor that leads to congestive heart failure.[6,7]

To of all of the above, one must add the fact that the elderly very frequently have associated diseases and take other drugs that can influence NSAID-induced toxicity. Because of this, the use of NSAID in high risk populations, such as the elderly, is of paramount interest and priority in our medium, and this is the objective of the following systemic review.

Material and Methods

A systematic review was carried out to analyze the security of NSAID use in the elderly. The selection criteria were:

1. Studies that included elderly individuals with pain of rheumatic origin of more than one month duration. An elderly individual was defined as a person with an age or mean age of >60 years.

2. Studies in which patients took any NSAID. There was no restriction regarding type and dose of the drug, nut studies in which the subjects took antiplatelet and non-analgesic/anti-inflammatory doses, as well as topical treatments were excluded.

3. To evaluate the efficacy of NSAID, articles that analyzed pain, function or quality of life of the elderly patients (no restriction regarding the type of variable used to measure these parameters was set). Then, and in order to evaluate the safety of NSAID, studies which included some of the following variables were included: gastrointestinal, renal,

TABLE 1. Search Strategy and Results in MEDLINE

	Search Strategy	Results
1	Search elderly OR aged OR Oldest Old OR Centenarians OR Centenarian OR Nonagenarians OR Nonagenarian OR Octogenarians OR Octogenarian OR Frail Elders OR Elders, Frail OR Frail Elder OR Frail Older Adults OR aging OR elder OR geriatric OR gerontology OR gerontological OR geriatrics	2 997 247
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	154 508
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	10 959
5	(Musculoskeletal diseases OR Polymyalgia Rheumatica OR Lupus Erythematosus, Systemic OR vasculitis OR polymyositis OR dermatomyositis) OR (musculoskeletal diseases [tiab] OR polymyalgia[tiab] OR "lupus erythematosus systemic"[tiab] OR vasculitis[tiab] OR polymyositis[tiab] OR dermatomyositis[tiab])	731 817
6	4 and 5	3081
7	acute [All Fields] OR post-operative [All Fields] OR post-surgical[All Fields] OR postsurgical [All Fields] OR Postoperative Complications [MeSH] OR Intraoperative Complications [MeSH] dysmenorrhoea[All Fields] OR orthodontic [All fields] OR Cancer OR neoplasm OR cancers OR tumor OR tumors OR Benign Neoplasms OR metastasis OR metastases	2 248 303
8	6 NOT 7	2855
9	8 Limits: 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, Aged: 65+ years, 80 and over: 80+ years	1549

or cardiovascular toxicity (no restriction was set regarding the type of variable used for their measurement either). *4*. With relation to the design of the studies, Jadad 4-5 clinical trials (CT) were included, as well as maximum quality cohorts. Studies with healthy volunteers, as well as studies in animals were excluded. Finally, with relation to the language, articles in English and Spanish were selected.

The following electronic databases were searched, up to December 2007: MEDLINE (from 1960), EMBASE (from 1980), and Cochrane Library (Central). Bot MeSH and free text formats were searched. No limits were set regarding the publication date. Specific search strategies are shown in Tables 1 and 2. No manual search was done of the abstracts from national (SER) or international (ACR, EULAR) meetings due to the high volume of articles recovered from electronic databases. A single reviewer analyzed the articles that resulted from the search strategy, as well as carried out a detailed analysis of the included ones. The result of the was first thinned by title and abstract or by the complete article in case they did nor have an abstract, in 20 minute sessions maximum time. After this process, the rest of the articles were analyzed in detail. Finally, a manual search with references from the selected articles was carried out for their detailed

TABLE 2. Search Strategy and Results in EMBASE

	Search Strategy	Results
1.	aged.mp. or aged/ or aged hospital patient.mp. or aged hospital patient/ or frail elderly.mp. or frail elderly/ or very elderly.mp. or very elderly/ or elder.mp. or geriatrics.mp. or geriatrics/ or aging.mp. or aging/	1 090 777
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.	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/	669 390
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	1 and 2 and 7 and 8	4449
11	10 not 9	2997
12	Limit 11 to humans	2965
13	Limit 12 to abstracts	2668

analysis. All of the references were recovered from the internet and introduced into the Procite 5.1 software for ease of management.
The methodological quality of the included studies was evaluated using: *a)* for the CT, the Jadad score[8] (1 to 5; good quality was considered as Jadad 3-5); and *b)* for the cohort studies, the Oxford quality score.

Results

Results of the search are detailed in Figure. Sixteen studies were finally included, which had more than 50 000 elderly patients, with a follow up which varied from 1 week to 4 years. A great diversity regarding the type of NSAID and the outcome measures was noted. Four metaanalysis (quality 1a-b), 9 CT (Jadad 4), 2 cohort studies (quality 2a), and 1 prevalence study (quality 2a). Most of the studies dealt with patients with osteoarthritis (OA) or rheumatoid arthritis (RA). Many studies did not allow for the use of gastric protection or did not note their use. The main results of the included studies are described in Table 3,[9-25] the excluded articles and the motive for exclusion, on Table 4.[26-106]
According to the evidence of the present systematic review, in general, NSAID have proven efficacious in the elderly for control of pain of rheumatic origin (resting, associated to movement, nocturnal), rigidity and joint function,[9,11-13,15,18,24] without being able to determine which NSAID has a better effect over others. Regarding adverse events, as for the adverse events, an increased risk is seen for any type of severe gastrointestinal event of any origin[11,12]: death or hospitalization,[23] digestive hemorrhage,[14,19,21] ulcer,[16,17,19-21,25] or gastric obstruction[19,21]; without being able to perform comparisons between all of the NSAID. This risk is reduced when a gastric protector is associated.[14,19-21] Regarding cardiovascular events, only the use of rofecoxib was associated to clinically significant edema and an increase in systemic blood pressure (BP).

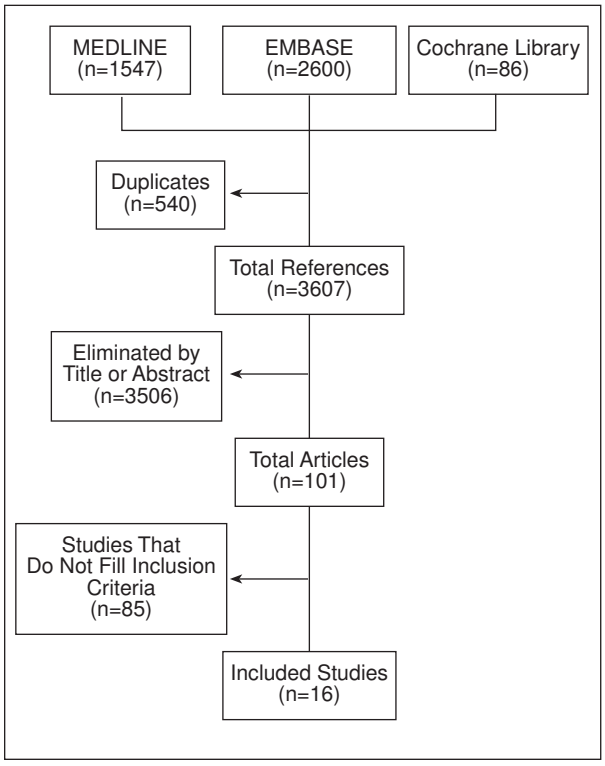

Figure. *Flow of the study selection*

Main Results of the Metaanalysis

According to Detora et al,[9] in the elderly with OA/RA, the use of rofecoxib (12.5/25 mg/day) was more effective than placebo for improving the global evaluation and pain when walking. Eisen et al[10] analyzed elderly patients with RA/OA in whom valdecoxib (10, 20, or 40 mg/day), in comparison with naproxen 1000 mg/day, ibuprophen 2400 mg/day, and diclofenac 150 mg/day, was associated with a reduced risk of moderate to severe gastrointestinal symptoms.
Lisse et al[11] showed that in elderly patients with OA, celecoxib (200 or 400 mg/day) or naproxen 1000 mg/day improved more the WOMAC index than placebo, without differences between them. There were no differences in the number of severe adverse events. Naproxen had a larger number of gastrointestinal adverse events than placebo and celecoxib 200 mg/day.
In the metaanalysis by Schiff et al,[12] in elderly OA patients, naproxen 1000 mg/day or ibuprophen 1200 mg/day improved pain during rest or with passive movements, nocturnal pain or pain when walking for 20 m and morning rigidity more than placebo. There were no differences in the number, type or severity of adverse events.

Main Results of the CT (Not Included in the Metanalysis)

Bakshi et al[13] analyzed elderly OA patients also who had received diclofenac 150 mg/day and showed superiority regarding resting, movement and pressure-induced pain and rigidity during rest when compared to placebo. There were no differences regarding pain during daily activity nor in the number of adverse events (mild-to-moderate).
Chan et al,[14] in elderly patients with arthritis and a previous ulcer, did not see any differences between celecoxib 400 mg/day and diclofenac 150 mg/day + omeprazole 20 mg/day in gastrointestinal bleeding, recurrent ulcer, or dyspepsia.
On the other hand, Earl et al,[15] in patients with OA, observed that ibuprophen 1600 mg/day or piroxicam 20

TABLE 3. Characteristics of the Included Studies[a]

Study	Participants and Intervention	Results
Bakshi et al,[13] CT double blind, placebo controlled. Follow-up, 4 months. Jadad 4	314 OA hip/knee/hands, 186 (60%) women, 60-80 years, mean duration of OA OA 6.4 years. CT: allergy to NSAID, ulcer or previous digestive bleeding, hepatic or blood disease or heart failure. Diclofenac 150 mg/day, 4 weeks (n=208). Placebo, 4 weeks (n=106)	Efficacy: in comparison with placebo, diclofenac was best in pain during rest (*P*<.001), pain on movement (*P*<.001), pain on local pressure (*P*=.040), resting stiffness (*P*=.008). No differences in daily activity. Safety: mild to moderate adverse events: diclofenac (n=30), placebo (n=18) (*P*=.551)
Chan et al,[14] CT double blind, placebo controlled. Follow up 6 months. Jadad 5	222 patients with arthritis (52% women; mean age, 67.1 years). IC: previously cured bleeding ulcer, *Helicobacter pilori* negative. EC: steroids, anticoagulants, gastric or duodenal surgery, erosive esophagitis, gastric obstruction, renal insufficiency. Celecoxib 400 mg/day + placebo 6 months (n=116). Diclofenac 150 mg/day + omeprazole 20 mg/day 6 months (n=106)	Security: *a)* gastrointestinal bleeding: celecoxib (n=7), diclofenac (n=9) (*P*=.511); *b)* recurrent gastroduodenal ulcer: celecoxib (n=20), diclofenac (n=26) (*P*=.180); *c)* absent to minimal dyspepsia: celecoxib (n=100), diclofenac (n=98) (*P*=.720); *d)* significant dyspepsia: celecoxib (n=16), diclofenac (n=18) (*P*=.572)
Cheatum et al,[25] transversal study, quality 2a	1826 patients (1009 AR, 817 OA), 67.3% women; mean age, 54.3 years. NSAID consumption	Security: *a)* prevalence of gastroduodenal ulcer: 60-69 years (29%), 70-79 years (34%), >80 years (32%); *b)* prevalence of gastroduodenal ulcer in RA: 60-69 years (24%), 70-79 years (27%),>80 years (14%); *c)* prevalence of gastroduodenal ulcer in OA: 60-69 years (35%),70-79 years (41%), >80 years (37%)
Detora et al,[9] metaanalysis, 3 EC (Jadad 4), follow up 6 weeks. Quality 1a	1491 OA (73% women; mean age, 62 years) Rofecoxib 12.5 mg/day 6 weeks (n=288). Rofecoxib 25 mg/day 6 weeks (n=607). Placebo 6 weeks (n=596)	Efficacy in comparison to placebo: *a)* global evaluation by the patient (VAS): rofecoxib 12.5 mg, –1(–1.3 to –1.8); rofecoxib 25 mg, –1.1 (–1.3 to –0.9), with no differences between both; *b)* pain on walking (VAS): rofecoxib 12.5 mg, –16.9 (–21.7 to –12.1); rofecoxib 25 mg, –18.1 (–22.8 to –13.4); no differences between both
Earl et al,[15] CT double blind, 4 week follow up. Jadad 5	59 OA (73% women; mean age, 71 years). IC: OA hip/knee, capable of walking and self-care. EC: treatments for pain different from NSAID, anemia, ulcer, alcohol, renal or hepatic disfunction. Ibuprophen 1600 mg/day 4 weeks (n=38). Piroxicam 20 mg/day 4 weeks (n=21)	Efficacy: only ibuprophen improves hip/knee flexion (*P*<.050). None: internal rotation of the hip; both: joint pain, hours of sleep (*P*>.050). Safety: adverse events: ibuprophen (n=6), piroxicam (n=7) (*P*>.050)
Eisen et al[10] (2005), metaanalysis, 5 CT (Jadad4-5), 12 week follow-up. Quality 1a	4394 RA/OA (28% women; mean age, 59 years). EC: severe gastrointestinal disease, malignancy. Valdecoxib 10-40 mg/day 12 weeks (n=2236). Other NSAID 12 weeks (n=1185): naproxen 1000 mg/day, ibuprophen 2400 mg/day, diclofenac 150 mg/day. Placebo 12 weeks (n=973)	Safety: compared with NSAID group risk of moderate/severe gastroduodenal symptoms; valdecoxib (any dose), HR=0.59 (95% CI, 0.47-0.74); valdecoxib 10 mg, HR=0.69 (95% CI, 0.53-0.90); valdecoxib 20 mg, HR=0.43 (95% CI, 0.32-0.60); valdecoxib 40 mg, HR=0.73 (95% CI, 0.49-1.08); placebo, HR=0.63 (95% CI, 0.47-0.83)
Fries et al[23] (1991), prospective cohort, mean follow up 4 years. Quality 2a	2747 RA (76.7% women; mean age, 60 years; mean duration of disease, 17 years). NSAID	Safety: *a)* risk of hospitalization/death due to adverse gastrointestinal event: >45 years, OR=7 (2.21-22.4); >50 years, OR=4.4 (2.01-9.52); >60 years, OR=2.7 (1.70-4.30); >65 years, OR=2.4 (1.56-3.55); >70 years, OR=2 (1.30-3.08); >75 years, OR=2.2 (1.28-3.85)
Hawkey et al,[16,17] EC a double blind, *double-dummy*, multicentric, 52 week follow up. Jadad 4	3959 OA, >65 years (76% women). IC: moderate joint pain. EC: gastric protectors, ulcer in the preceding 30 days, bleeding/perforation/intestinal obstruction. Lumiracoxib 400 mg/day(n=3980). Naproxen 1000 mg/day (n=2098). Ibuprophen 2400 mg/day (n=1861)	Safety: risk of gastroduodenal ulcer: NSAID, HR=1.79 (1.33-2.42); lumiracoxib, HR=1.26 (0.82-1.95)
Kaarela et al,[18] CT double blind, 14 day follow up. Jadad 4	31 RA (84% women), 18 >65 years. Indomethacin 150 mg/day 14 days	Efficacy: improvement of morning stiffness (*P*=.001), no differences in comparison with younger persons

TABLE 3. Characteristics of the Included Studies[a] *(Continuation)*

Study	Participants and Intervention	Results
Koch et al,[19] CT double placebo, 6 month follow up. Jadad 4	8840 RA (women; mean age, 68 years). IC: >52 years, NSAID for 6 months. EC: peptic ulcer 30 days previous, other severe digestive diseases, hemorrhagic problems. NSAID + misoprostole 6 months n=4404). NSAID + placebo 6 months (n=4404)	Safety: controlled blind risk of gastrointestinal complication with (ulcer, hemorrhage, obstruction) >65 years. Group with misoprostole, RR=0.70; placebo, RR=1.16 (risk reduction of 40%)
Le Loet,[24] prospective, multicentric cohort, 4 week follow-up. Quality 2a	19 880 patients >60 years (mean, 72 years), 66% women with rheumatic disease (93% degenerative disease). EC: contraindications to the use of NSAID, severe liver, renal or blood disease. Ketoprophen 400 mg/day 4 weeks	Efficacy: *a)* GPE good/excellent, 74.4%; *b)* tolerance according to the patient good/excellent, 85%. Safety: *a)* adverse events: ketoprophen, 15.3%
Lisse et al,[11] metaanalysis, 3 CT (Jadad 3-4), 12 week follow-up. Quality 1b	786 hip or knee OA, >70 years, 68% women. Celecoxib 200 mg/day 12 weeks (n=191). Celecoxib 400 mg/day (n=183). Naproxen 1000 mg/day 12 weeks (n=206). Placebo 12 weeks (n=188)	Efficacy: compared to placebo the 3 NSAID improved the WOMAC (P<.001) and SF-36 (P<.010). No differences between 3 NSAID. Safety: *a)* at least one severe adverse event: celecoxib 200 mg (n=7), celecoxib 400 (n=9), naproxen 1000 mg (n=4), placebo (n=8) (P>.050); *b)* gastrointestinal adverse event: celecoxib 200 mg (n=49), celecoxib 400 mg (n=37), naproxen (n=62), placebo (n=32). More in naproxen compared to placebo and celecoxib 200 mg
Regula et al[20] (2006), CT double blind, 6 month follow-up. Jadad: 4	595 RA, OA, spondylosis, spondilytis (71% women; mean age, 66 years). IC: ≥1 factor of gastrointestinal toxicity. EC: active/complicated ulcer, digestive surgery, esophageal adherences, Zollinger-Ellison, severe disease. NSAID + pantoprazole 20 mg/day 6 months (n=196). NSAID + pantoprazole 40 mg/day 6 months (n=199). NSAID + omeprazole 20 mg/day 6 months (n=200)	Safety: Peptic ulcer: pantoprazole 20 mg/day (n=7), pantoprazole 40 mg/day (n=3), omeprazole 20 mg/day (n=4) (P>.050); no differences: gastrointestinal symptoms, reflux esophagitis, 10 or more erosions or petequiae, severe adverse events
Schiff et al,[12] metaanalysis of 2 CT (Jadad 4), 1 week follow-up. Quality 1b	198 knee OA, >65 years, 62% women. IC: active O with at least moderate pain. EC: gastric protectors, other rheumatic disease, history of peptic ulcer in the previous 9 months, digestive surgery, absorption problems. Naproxen 400 mg/day 1 week (n=66). Ibuprophen 1200 mg/day 1 week (n=66). Placebo 1 week (n=66)	Efficacy: naproxen and ibuprophen better than placebo in: resting pain, passive nocturnal movements, morning stiffness, time for walking 20 m (P<.050), daily pain (P<.010), on weight lifting (P=.064). Safety: *a)* any adverse event: naproxen 440 mg/day (n=14), ibuprophen 1200 mg/day (n=14), placebo (n=17) (P=.538); *b)* severe adverse events: naproxen 440 mg/day (n=3), ibuprophen 1200 mg/day (n=4), placebo (n=8) (P=.115); *c)* gastrointestinal adverse events: naproxen 440 mg/day (n=11), ibuprophen 1200 mg/day (n=10), placebo (n=9) (P=.627)
Silverstein et al,[21] CT double blind, controlled with placebo, 6 month follow-up. Jadad 4	8840 RA (women; mean age, 68 years). IC: >52 years, 6 months of NSAID use. EC: ulcer in previous 30 days, severe digestive diseases, gastric protectors, hemorrhagic problems. NSAID + misoprostole 6 months (n=4404). NSAID + placebo 6 months (n=4404)	Safety: association (adjusted) to gastrointestinal complication (ulcer, hemorrhage, obstruction) in >75 years in the cohort (OR=2.48; 95% CI, 1.48-4.14)
Whelton et al,[22] CT double blind, 6 week follow-up. Jadad 5	1092 OA (62% women; mean age 73 years). IC: >65 years, OA functional class I-III, stable AHT with fixed antihypertensive medication dose during previous 3 months, benefit from NSAID. EC: gastric protectorss, severe disease. Celecoxib 200 mg/day 6 weeks (n=543). Rofecoxib 25 mg/day 6 weeks (n=549)	Safety: a) ↑ in SBP >20 and SBP >140 mm Hg: celecoxib (n=38), rofecoxib (n=81) (P<.001); b) ↑ in DBP >15 and DBP >90 mm Hg: celecoxib (n=7), rofecoxib (n=12) (P=.257); c) clinically significant edema: celecoxib (n=26), rofecoxib (n=42) P=.045); d) congestive heart failure (first episode): (celecoxib (n=2), rofecoxib (n = 3) (P=.663)

[a]AHT indicates arterial hypertension; BP, blood pressure; CI, confidence interval; CT, clinical trial; DBP, diastolic blood pressure; EC, exclusion criteria; HZ, hazard ratio; IC, inclusion criteria; NSAID, non steroidal anti-inflammatory drugs; OA, osteoarthritis; OR, odds ratio; PGE, physicians global evaluation; RA, rheumatoid arthritis; RR, relative risk; SBP, systolic blood pressure.

TABLE 4. Excluded Studies and Causes for Exclusion

Study	Causes for Exclusion
Admani et al[26] (1983)	Insufficient quality of the study
Ahern et al[27] (1992)	Insufficient quality of the study
Arone[28] (1989)	Insufficient quality of the study
Bacon[29] (1994)	Insufficient quality of the study
Bauer et al[30] (1996)	Insufficient quality of the study
Blardi et al[31] (1992)	Insufficient quality of the study
Browning et al[32] (1994)	Insufficient quality of the study
Busson[33] (1986a)	Insufficient quality of the study
Busson[34] (1986b)	Insufficient quality of the study
Calin[35] (1993)	Insufficient quality of the study
Caughey et al[36] (1989)	Insufficient quality of the study
Cordaro et al[37] (1988)	No data in patients over 60
Cummings et al[38] (1988)	Insufficient quality of the study
Currie et al[39] (1984)	Insufficient quality of the study
Davis et al[40] (1987)	Insufficient quality of the study
Dominick et al[41] (2003)	Not related to research question
Dreiser et al[42] (1993)	Insufficient quality of the study
Famaey et al[43] (1976)	Insufficient quality of the study
Fossaluzza et al[44] (1989)	Insufficient quality of the study
Fries[45] (1992)	Does not strictly analyze patients over 60
Fries et al[46] (2004)	Not related to research question
Fullerton et al[47] (1993)	Insufficient quality of the study
Gabriel et al[48] (1997)	Insufficient quality of the study
Geczy et al[49] (1987)	Insufficient quality of the study
Girawan et al[50] (2004)	Insufficient quality of the study
Goldstein et al[3] (2003)	Healthy subjects
Grace et al[51] (1987)	Insufficient quality of the study
Grigor et al[52] (1987)	Unclear wether ASA is used as antiplatelet, analgesic, or anti-inflammatory
Halici et al[53] (2002)	Insufficient quality of the study
Hart et al[54] (1965)	Insufficient quality of the study
Hart et al[55] (1983)	Insufficient quality of the study
Hawkey et al[56] (2001) 60	Not enough data in patients over
Henry et al[57] (1997)	Insufficient quality of the study
Hochain et al[58] (1995)	Insufficient quality of the study
Horackova et al[59] (2005)	Insufficient quality of the study
Innes[60] (1977)	Insufficient quality of the study
Jackson et al[61] (1987)	No concrete data in patients over 60
Janke et al[62] (1984)	Insufficient quality of the study
Johnson et al[63] (1993)	Insufficient quality of the study
Laine et al[64] (2002)	Insufficient quality of the study
Lai et al[65] (2005)	Insufficient quality of the study
Lane et al[66] (1997)	Insufficient quality of the study
Layton et al[67] (2003)	Insufficient quality of the study
Le Loet et al[68] (1997)	Insufficient quality of the study
Littman et al[69] (1995)	Insufficient quality of the study
Mamdani et al[70] (2002)	Insufficient quality of the study
Mann et al[71] (2004)	General population is studied
McNeil[72] (1993)	Insufficient quality of the study
Meurice[73] (1983)	Insufficient quality of the study
Montrone et al[74] (1990)	Insufficient quality of the study
Morgan et al[75] (1993)	Insufficient quality of the study
Morgan et al[2] (2001)	Insufficient quality of the study
Morton et al[76] (1998)	No concrete data in patients over 60
Motsko et al[77] (2006) General population	Insufficient quality of the study.
Nesher et al[78] (1995)	Insufficient quality of the study
Niccoli et al[7] (2002)	Insufficient quality of the study
Nietert et al[79] (2003)	Insufficient quality of the study
O'Brien[80] (1983)	Insufficient quality of the study
Perpignano et al[81] (1994)	Insufficient quality of the study
Puccetti et al[82] (1991)	Insufficient quality of the study
Rabenda et al[83] (2005)	General population under study
Rabenda et al[84] (2006)	No concrete data in patients over 60
Rahme et al[85] (2002)	Insufficient quality of the study
Rahme et al[86] (2007a)	Insufficient quality of the study
Rahme et al[87] (2007b)	Insufficient quality of the study
Roth et al[88] (1993)	Insufficient quality of the study
Roth et al[89] (1995)	Insufficient quality of the study
Scharf et al[90] (1998)	Insufficient quality of the study

TABLE 4. Excluded Studies and Causes for Exclusion *(Continuation)*

Study	Causes for Exclusion
Schattenkirchner[91] (1991)	Insufficient quality of the study
Schattenkirchner[92] (1993)	Insufficient quality of the study
Sheldon et al[93] (2005)	No concrete data in patients over 60
Sheridan et al[94] (2005)	Insufficient quality of the study
Smalley et al[95] (1995)	Insufficient quality of the study. General population.
Sontag et al[96] (1994)	Does not strictly analyze patients over 60
Stewart et al[97] (1988)	Insufficient quality of the study
Theiler et al[98] (2002)	Insufficient quality of the study
Todesco et al[99] (1994)	Insufficient quality of the study
Truitt et al[100] (2001)	Insufficient quality of the study
Vetter[101] (1985)	Insufficient quality of the study
Vonkeman et al[102] (2007)	Insufficient quality of the study
Whelton et al[103] (2006) over 60	Does not strictly analyze patients
Williams[104] (1985)	Insufficient quality of the study
Williams et al[105] (1989)	Insufficient quality of the study
Yajima et al[106] (2007)	Insufficient quality of the study

mg/day improved joint pain and hours of sleep. Only ibuprophen improved hip and knee flexion and none improved internal rotation of the hip. There were no differences in the number of adverse events or treatment abandonment in the NSAID group.

According to Hawkey et al,[16,17] in elderly patients with OA, lumiracoxib 400 mg/day was not associated with a gastroduodenal ulcer, but naproxen 1000 mg/day and ibupropheno 2400 mg/day were.

In the study by Kareela et al,[18] elderly patients with RA and treated with indomethacin 150 mg/day improved their morning stiffness. There were no differences when compared to patients under 65.

According to Koch et al,[19] elderly patients with RA undergoing routine treatment wit NSAID + misoprostol, reduced in 40% the risk of severe gastrointestinal complications when compared to NSAID by itself.

Regula et al[20] studied elderly patients with RA/OA treated with NSAID + pantoprazole 20 or 40 mg/day or omeprazole 20 mg/day, without observing any differences in the appearance of mild or severe gastrointestinal adverse events.

In the CT by Silverstein et al,[21] elderly patients with RA using NSAID had an association to a larger risk of severe adverse events (ulcer, hemorrhage, obstruction), odds ratio [OR] = 2.48 (interval, 1.48-4.14).

Whelton et al,[22] in elderly patients with OA, did not find differences in the increase of diastolic BP nor in the appearance of heart failure (first episode) among those taking celecoxib 200 mg/day or rofecoxib 25 mg/day. there were more patients presenting clinically significant edema and an increase in systolic BP than in the rofecoxib group.

Main Results From the Cohort Studies

In the study by Fries et al[23] the risk of hospitalization or death due to a gastrointestinal event associated to NSAID in patients with RA was: in those older than 60, OR=2.7; older than 65, OR=2.4; older than 70, OR=2.0, and in older than 75, OR=2.2 (all of the results were statistically significant).

In the Le Loet[24] cohort, in elderly patients with rheumatic disease who had taken ketoprophen 400 mg/day, the physicians global evaluation was good/excellent in 74.4% and, according to patients, tolerance to the drug was good/excellent in 85%, There were drug-related adverse events in 15.3% of patients.

Prevalence Study

Cheatum et al,[25] in patients with RA/OA treated with NSAID showed that the prevalence of gastroduodenal ulcer was: in the 60-69 years of age group, 29%; in the 70-79 group, 34%; and in those over 80, 32%.

Discussion

We have analyzed the results of clinical efficacy (in treatment of pain and quality of life) and safety (gastrointestinal, cardiovascular, renal) of NSAID in the treatment of rheumatic disease in the elderly, through a systematic review of the literature. The objective is to contribute to the clinical evidence published when generating consensus on the use of NSAID in the elderly.

Regarding efficacy, according to the results obtained, there is data that supports the use of NSAID for pain and other symptoms with a rheumatic origin in the elderly.[9,11-13,15,18,24] But, given the diversity of NSAID employed in the studies and the different variables employed to measure efficacy, it is difficult to define wether a NSAID is clearly more advantageous than another in the elderly with pain of rheumatic origin. The magnitude of their effects in general is clearly, and according to data published, not very interesting although the context in which they are used

must be taken into account (mainly elderly patients with rheumatoid arthritis and OA).

Regarding their safety, one must first mention that, according to a transverse study,[25] the prevalence of gastroduodenal ulcer elderly patients with rheumatic disease treated with NSAID is considerably larger in the 70-79 years of age group. This fact is complemented with data from a cohort study and other CT in which evidence of an increased risk of any kind of severe adverse event, especially gastrointestinal in origin (hospitalization or death,[23] digestive hemorrhage,[14,19,21] ulcer,[16,17,19-21,25] or digestive obstruction[19,21]). In general population studies, the risk described of severe gastrointestinal events is even larger.[3] This could be due to the fact that currently, in rheumatology, NSAID are prescribed to the elderly at the moment of acute pain and not so much as a continuous, chronic treatment. Only one article of those included analyzed cardiovascular adverse events,[22] showing no significant differences in diastolic BP increase nor in the appearance of heart failure (first episode) between celecoxib and rofecoxib. But there were more patients with clinically significant edema and an increase in diastolic BP in the rofecoxib group. Once again, it is difficult to establish what NSAID presents a better security profile.

Lastly, it must be mentioned that the articles selected the use of gastroprotection was associated to a reduction in the risk of gastroduodenal ulcer in the elderly.[19-21] Although as happens with efficacy and security, it is difficult to establish which one is better than the others.

But all of these results must be taken cautiously due to the following motives: one of the main difficulties in the review has been the lack of a homogeneous definition of the concept of elderly, in other words, at what age and/or conditions do we consider a human being as being elderly. Another added difficulty is that, in general, in CT and other studies, the number of included elderly subjects tends to be low, with a consequent scarcity in data regarding them, therefore leading to an incorrect description of what happens in daily clinical practice with this population. In the present review, a cutpoint of 60 years of age was established, taking into account that it may be different (regarding efficacy and safety of NSAID) to have 60 or 79 years of age. And, as has been observed, there are few analysis of age subgroups among the elderly, that might study this phenomenon. Another possible limitation is that the difficulty to adjust all of the variables in which could influence the elderly patient with rheumatic disease, could render the results variable, modifying the results exposed above (concomitant use of other drugs, other diseases, etc). Lastly, there is also a lack of studies that confirm the effects on renal and cardiac function in elderly persons on NSAID, in literature already published and other populations.

In conclusion, NSAID are effective in the elderly for the treatment of pain of rheumatic origin, even if the risk of an adverse event is larger, making it recommendable, on the one hand, to employ gastroprotection in every case, apart from individualizing every case of NSAID use, taking into account that alternatives to treatment for pain of rheumatic origin are available and have proven to be safe and effective in the elderly, such as analgesics or low-dose steroids.

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