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REVIEW

Hepatotoxicity induced by coxibs: how concerned should we be?

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ABSTRACT

Introduction: The selective inhibitors of COX-2, coxibs, are nonsteroidal anti-inflammatory drugs (NSAIDs) that have much better gastrointestinal safety profile as compared with non-selective NSAIDs. In this review, we analyze both the epidemiological features of coxib-induced hepatotoxicity and the clinical impact of coxib-associated liver damage, based on literature data.

Areas covered: We carried out a search of the databases MEDLINE (PubMed), LILACS and SCIELO, from December 1999 to January 2016, to retrieve studies exploring the real impact of coxibs in liver toxicity as compared to non-selective COX-2 inhibitor NSAIDs.

Expert opinion: Although reliable data on the incidence of celecoxib- and etoricoxib-induced hepatotoxicity are lacking, because of cohort studies have been generally underpowered to detect hepatic events, coxibs have been scarcely related to hepatotoxicity. Hence, coxib-induced liver injury seems to be an uncommon event, yet exhibits a wide spectrum of damage. Increasing COX-2 drug selectivity, as for rofecoxib, valdecoxib, parecoxib, and lumiracoxib, has been associated with higher cardiovascular risk, as well as dermatological and serious hepatic reactions. The actual risk of liver toxicity from the currently approved coxibs compared with non-selective NSAIDs will be discussed. Finally, classical and novel molecular mechanisms of coxib-induced hepatotoxicity are also described.

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1. Introduction

Coxibs, highly selective inhibitors of cyclooxygenase 2 (COX-2), have gained worldwide popularity due to improved tolerance and gastrointestinal safety profile when compared to nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) [1,2]. Actually, the selective COX-2 inhibitors rofecoxib and celecoxib caused significantly less gastroduodenal ulceration than classic NSAIDs in patients with osteoarthritis or rheumatoid arthritis, while displaying equivalent anti-inflammatory and analgesic efficacy [3,4]. Chemical structures of selective and nonselective COX-2 inhibitors are shown in Figure 1.

Of note, 4 out of 6 drugs belonging to this group have already been withdrawn from the market due to serious adverse events (Table 1). This situation probably reflects the limitation of post-marketing studies, which failed to include the sufficient number of exposed subjects required to identify rare, unpredictable adverse reactions once the drug had been launched into the market.

The link between intake of rofecoxib, and later on of other NSAIDs, and the occurrence of cardiovascular adverse events became apparent over the last decade [5,6]. Due to the high risk of myocardial infarction and blood hypertension related to rofecoxib use, the drug was withdrawn from the pharmaceutical market in 2004 by its manufacturer (Merck & Co., Inc.) [7]. In addition, valdecoxib and its prodrug, parecoxib, were also voluntarily withdrawn by the manufacturer (Bextra, Pfizer Canada Inc.) and banned by the Food and Drug Administration (FDA) in 2005 due to severe dermatological reactions [8]. Parecoxib showed initial evidence of increased cardiovascular risk in a significant number of cases reported by Nussmeier et al. [9], who conducted a randomized, double-blind study in 1671 subjects. Patients were randomized into three treatment arms: (1) intravenous parecoxib followed by oral valdecoxib, (2) valdecoxib plus placebo, and (3) placebo alone. The group treated with valdecoxib and parecoxib showed a higher and significant rate of serious cardiovascular events as compared to placebo (myocardial infarction, pulmonary thromboembolism, and cardiac arrest). All cases of severe dermatological injury were associated with an apparent immunoallergic etiology, including several reports of Stevens–Johnson syndrome, and contributed to the permanent withdrawal of these compounds from the market by the FDA [8], the European Medicines Agency (EMA) [10], and the National Administration of Drugs, Food, and Medical Technology (ANMAT) in Argentina, in April 2005 [11]. Celecoxib and etoricoxib are the only two

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Article highlights

- The discovery of coxibs is not a complete success because of the cardiovascular (rofecoxib, valdecoxib, and parecoxib) and hepatic toxicity (lumiracoxib) that led to market withdrawal.
- Celecoxib and etoricoxib are widely used due to their favorable benefit-to-risk profile.
- Celecoxib is associated with cholestatic hepatitis, and although cases of etoricoxib-induced liver damage have not been published so far, its hepatotoxic potential is recorded in the summary of product.
- Accumulated evidence suggests that hepatotoxicity of the currently approved coxibs, celecoxib and etoricoxib, is less frequent than that of non-selective NSAIDs.

This box summarizes key points contained in the article.

members of this pharmacological group that continue to be marketed in many countries in the world.

Laine et al. [12] carried out recently a systematic review of the literature, in which they analyzed controlled trials, meta-analyses, and reviews related to the safety profile of selective inhibitors of COX-2 in patients with osteoarthritis. They showed that, when coxibs are used to treat moderate to severe pain, its therapeutic efficacy was similar to the remaining NSAIDs, and higher than that observed with paracetamol. When the authors selectively analyzed meta-analyses, they documented that 74% of coxibs showed lower risk of gastrointestinal complications as compared to the remaining NSAIDs, but the rate of myocardial infarction risk was twice that in placebo- and naproxen-treated patients. There were no differences in cardiovascular risk when coxibs were compared to NSAIDs or naproxen [12]. In spite of these conflicting results, the FDA reported several years ago a slight increase in the cardiovascular risk originated by the use of coxibs [13].

Hepatotoxicity induced by these drugs shows a wide range of variability. There have been reports of severe hepatitis and acute liver failure induced by lumiracoxib, which led to its permanent withdrawal from the pharmaceutical market [14–16]. The currently marketed compounds, celecoxib and etoricoxib, seem to be associated with a lesser risk of liver damage, even though quality of the data available is limited to define an accurate incidence. There are some reports of cholestatic hepatitis induced by celecoxib [17–26], and the hepatotoxic potential of etoricoxib is recorded in the summary of the product characteristics. Hepatotoxicity and the liver safety profile linked to the use of the currently labeled coxibs will be discussed deeply here. Finally, classical and novel molecular mechanisms of coxib-induced hepatotoxicity reported in the literature, including genetic susceptibility to coxib-induced liver damage, are also critically discussed.

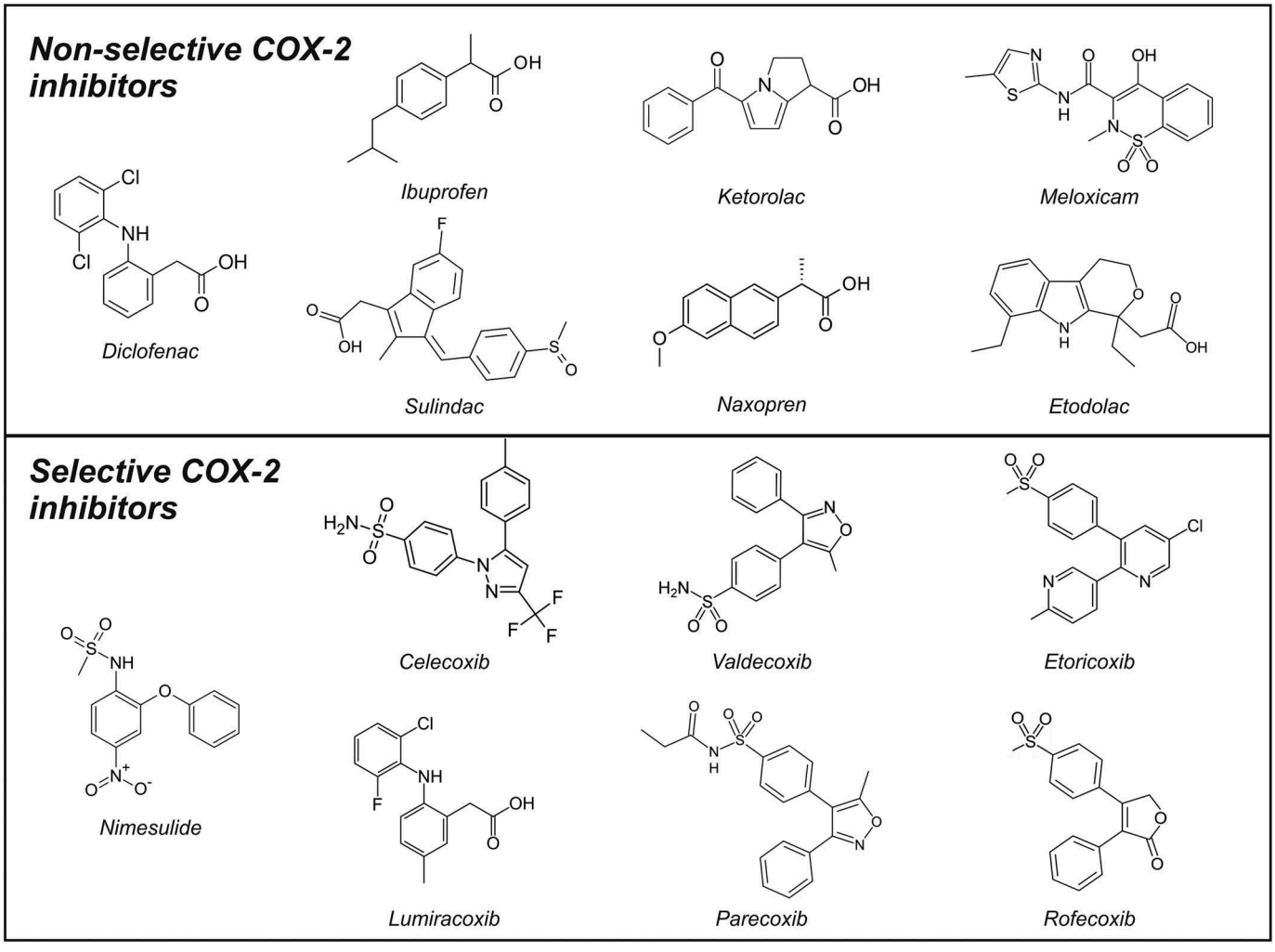

Figure 1. Chemical structures of selective and non selective COX-2 inhibitors.

Table 1. Classification of both currently in use and coxibs withdrawn from the market.

Drug name	Status	Withdrawal reason
First generation (approved since 1999)		
Celecoxib	Currently in use	
Rofecoxib	Withdrawn in 2004	Cardiovascular events (MHA/AH)
Second generation (approved since 2002)		
Valdecoxib	Withdrawn in 2005	Cardiovascular events and severe dermatological injury
Parecoxib	Withdrawn in 2005	Cardiovascular events
Lumiracoxib	Withdrawn in 2007	Severe liver damage
Etoricoxib	Currently in use	

2. Methods

We performed a search of the databases MEDLINE (PubMed), LILACS, and SCIELO, from December 1999 to January 2016, to collect studies using tools to assess the potential significance of an individual PI, using the search terms 'coxibs,' or 'celecoxibs,' or 'lumiracoxib,' or 'etoricoxib,' or 'valdecoxib,' or 'rofecoxib,' or 'parecoxib,' or 'selective COX2 inhibitors,' or 'nonselective COX2 inhibitors,' or 'nonsteroidal anti-inflammatory drugs,' in association with the search terms 'hepatotoxicity,' or 'hepatitis,' or 'cholestasis,' or 'liver failure,' or 'liver damage,' or 'liver toxicity,' or 'liver injury,' Moreover, we identified cases included in the Spanish Registry of Hepatotoxicity and Latin-American Network of Hepatotoxicity (LATINDILIN). The inclusion criteria were as follows: (1) Case reports and series of patients suffering from hepatotoxic events while taking coxibs, where phenotypic, histological, and/or pharmacogenetic data were included, and (2) studies relevant to the pathomechanisms by which coxibs exert hepatotoxicity, either in humans or animal models.

3. Phenotypic features of coxib-induced hepatotoxicity

Table 2 shows all case reports and small series of patients associated with liver toxicity induced by coxibs published so far in the literature [17–35].

The frequency of coxib-induced hepatotoxicity is not defined. Well-documented cases of acute hepatitis or cholestatic hepatitis have been published with celecoxib and rofecoxib [17–33]. Studies have been carried out by using different methodological designs. However, most findings are consistent in showing a lower prevalence of liver reactions when compared coxibs with the remaining NSAIDs (see Table 3).

Laine et al. [12], when analyzing data from 7 population-based studies and 100 randomized controlled trials involving NSAIDs, reported on an increase in serum aminotransferases with rofecoxib (2%) and lumiracoxib (3%), but failed to identify any significant increases in clinical liver events. Sulindac and nimesulide were associated with a higher risk of hospitalization due to liver damage. However, Lee et al. [40], when evaluating the risk of acute hepatic damage induced by NSAIDs, found that the hospitalization risk with celecoxib (odds ratio (OR) = 1.92, 95% CI = 1.38, 2.69) was similar to that of other nonselective NSAIDs (OR = 2.13, 95% CI = 2.00, 2.28).

Another study analyzed the proportions of hepatic adverse drug reactions associated with NSAIDs in France, where the information from French pharmacovigilance databases was obtained from 1982 to 2001. The risk was very high for clometacin, followed by sulindac, and it was slightly lower for naproxen, diclofenac, piroxicam, and tenoxicam. Last on the list, due to their lower risk of liver damage, were celecoxib and rofecoxib, with only 6 and 3 reported cases, respectively [41].

Rostom et al. [42] searched in public FDA archives, MEDLINE, and EMBASE for randomized controlled trials using ibuprofen, diclofenac, meloxicam, naproxen, rofecoxib, celecoxib, and valdecoxib in adults with rheumatoid arthritis or osteoarthritis. They searched for transaminase elevations > 3 upper limit of normal (ULN), serious hepatic adverse events, liver-related drug withdrawal, hospitalizations, and death. From 65 database articles and 67 FDA-submitted studies, they concluded that patients on diclofenac and rofecoxib had a higher level of transaminases as compared with both placebo and other NSAIDs. Interestingly, only one case of hospitalization associated with naproxen was reported among 37,671 patients from studies computing this incident; this represents an incidence of 3 in 100,000 patients. Similarly, only one patient died due to naproxen-induced liver toxicity among 51,942 patients consuming NSAIDs, which also represents a low death rate (2 in 100,000 patients).

Traversa et al. [37] carried out a retrospective study in Umbria (Italy), a region with 850,000 inhabitants, where 2 million prescriptions of NSAIDs had been made through a 5-year period (1997–2001). They found that the risk of NSAID-induced hepatotoxicity was very small. Indeed, the incidence of liver injury was 1.7 in 100,000 exposed individuals, referred to the number of prescriptions. A higher hepatotoxicity rate was recorded among people older than 75 years (5.7-fold higher risk of liver disease as compared with people younger than 45 years). Noteworthy, only one case of celecoxib-induced liver injury was reported. However, this study included data from 1997 to 2001, when coxibs had just gained marketing approval, and therefore their hepatotoxicity figures could have been underrepresented.

Our Latin American hepatotoxicity registry (LATINDILI) has been working since 2011, and has received over 200 cases of hepatotoxicity due to drugs or herbal supplements among different Latin American countries [43]. The main goal of this registry is the identification in a prospective and standardized manner of the different features that drug-induced liver disease have in Latin America, including the most frequent culprit drugs/herbal supplements, patient characteristics, phenotypicity, and outcome. The registry is also aimed to contribute to establish the local hepatotoxicity rates for these drugs, and their comparison with data from other registries [44]. Nimesulide and diclofenac lead the list of NSAIDs included in LATINDILI network, and only one of these cases was associated with coxib administration; the drug responsible for this adverse effect was etoricoxib, and showed a hepatocellular pattern. On the other hand, in the Spanish registry, which has included more than 800 cases so far, ibuprofen heads the NSAID list, followed by diclofenac and nimesulide,

Table 2. Case reports and series of coxib-induced hepatotoxicity.

Author, year, reference	Sex, age (year)	Indication, dose, and latency	Symptoms	Liver test at presentation (times over normal value)	Histological findings	Resolution
Celecoxib						
Nachimuthu et al. 2001 [17]	F, 67	Osteoarthritis; 200 mg/d, 1 week	Jaundice	TB 5, ALP 1.2, ALT 21	Not done	0.5 month
Galan et al. 2001 [18]	F, 55	Radiculopathy pain; 200 mg/d, 3 weeks	Jaundice and pruritic rash	TB 12, ALP 2,8, ALT 87	Marked intrahepatocyte cholestasis associated with rich eosinophilic inflammation involving portal tracts	4 months
O'Beirne et al. 2001 [19]	F, 54	Sacroiliac pain; 200 mg/d, 2 days	Jaundice, pruritus, and dark urine	TB 6.15, ALP 2, ALT 41	Not done	3 weeks
Grieco et al. 2002 [20]	M, 41	Knee pain; 200 mg/d, 3 days	Jaundice, malaise, and pruritus	TB 8, ALT 6	Cholestasis with bile plugs in dilated bile canaliculi and mild portal infiltrate of polymorphonuclear, eosinophilic, and mononuclear leukocytes	3 weeks
Alegria et al. 2002 [21]	M, 49	Minor musculoskeletal pain; 200 mg/d, 2 weeks	Jaundice, fatigue, dark urine	TB 31, ALP 2, ALT 2	Cirrhosis, mononuclear infiltration of the portal triad. Marked hepatocellular cholestasis	12 months
Chamouard et al. 2005 [22]	F, 32	Pain following a surgery; 200 mg/d, 24 days	Jaundice and pruritus	TB 19, ALP 5.5, ALT 1.6	Marked canalicular and hepatocyte cholestasis. Bile plugs without bile duct injury and hyperplasia	18 months
El Hajj et al. 2009 [23]	F, 52	Muscle ache and pain; 200 mg/d, 1 week	Pruritus and dark urine	TB 10.8, ALP 5.5, ALT 3.6	Ductopenia with lobular foam cell change and cholestasis along with periportal fibrosis. No bridging fibrosis	LT, 2 months
Famularo et al. 2012 [24]	F, 77	Gout attack; 400 mg/d, 12 days	Fatigue, abdominal discomfort	TB 2.4, ALP 2,4, AL 11	Not done	1 week
Nayudu et al. 2013 [25]	F, 34	Pain after a gynecological procedure, 3 weeks	Jaundice and epigastric pain	TB 3.4, ALP 1.5, ALT 10	Periductal fibrosis and findings suggestive of sclerosing cholangitis	1 month
Judson et al. 2014 [26]	F, 28	Knee pain; 200 mg/d, 13 days	Jaundice and pruritus	TB 3.9, ALP 1, ALT 6	Extensive canalicular and hepatocyte cholestasis. No fibrosis, no bile duct injury or loss, no inflammation or steatosis	7 months
Rofecoxib						
Huster et al. 2002 [27]	F,52	Osteoarthritis; 25 mg/d, 12 weeks	Jaundice, pruritus and malaise	TB 25, ALP 7, ALT 9.5	Marked canalicular and hepatocyte cholestasis, rich eosinophil inflammation involving portal tracts	2,5 months MARS +UDCA
Harsch et al. 2003 [28]	F, 73	Cervical spine pain, 25 mg/d, 10 days	Jaundice, pruritus and weakness	TB 20, ALP, 2,7, ALT 26	Distinct inflammatory portal infiltration with lymphocytic and eosinophilic reaction. Marked hepatocellular and canalicular cholestasis	2 months
Linares et al. 2004 [29]	F, 74	Musculoskeletal pain; 12,5 mg/d, 8 weeks	Jaundice, dark urine and renal failure	TB 12, ALP 14, ALT N	Marked centrilobular cholestasis, without areas of hepatocyte necrosis, fibrosis or hepatic granulomas	48 months, UDCA + prednisona
Papachristou et al. 2004 [30]	F, 76	Osteoarthritis; 25 mg/d, 22 months	Jaundice, dark urine and pruritus	TB 6, ALP 2.5, ALT 6	Moderate hepatocellular and intracanalicular cholestasis. Focal lymphocytic bile duct inflammation with mild lymphocytic bile damage and minimal ductular proliferation	3 months
Haider et al. 2005 [31]	M, 62	Non specific foot pain; 6 months	Jaundice and pruritus	TB 12,ALP 1.5, ALT N	Cholestasis and mixed neutrophil and eosinophil infiltrate within the periportal areas	1 month, UDCA hemodialysis (ARF)
Ouar et al. 2005 [32]	F, 69	Left shoulder pain; 12,5 mg/d, 4 weeks	Jaundice	TB 18, ALP 4, ALT 42	Moderate ductal proliferation. Inflammatory portal infiltration with lymphocytes and plasma cells. Portal and periportal fibrosis	6 months

(*Continued*)

Table 2. (Continued).

Author, year, reference	Sex, age (year)	Indication, dose, and latency	Symptoms	Liver test at presentation (times over normal value)	Histological findings	Resolution
Yan et al. 2006 [33]	M, 44	Osteoarthritis; 25 mg/d, 2 weeks	Jaundice, nausea, and malaise	TB 14, ALP 5, ALT 30	Mononuclear infiltration within the portal triad and perivenular areas. Mild hepatocellular necrosis and moderate interface hepatitis. Isolated eosinophils. Cholestasis was not evident	2 months (UDCA)
	F, 44	Arthralgia; 12,5 mg/d, 8 weeks	Jaundice, pruritus and dark urine	TB 12,ALP 1.6, ALT 16	Mild macrovesicular steatosis, portal and perivenular fibrosis. Mononuclear inflammatory infiltrate in a portal and lobular distribution	1 month
Lumiracoxib						
Pillans et al. 2012 [34]	F, 63	Osteoarthritis; 200 mg/d, 3 months	Jaundice and dark urine	TB 16, ALP 5, ALT 75	Sub-massive hepatic necrosis (bridging necrosis). Neutrophilic infiltrate, occasional eosinophils	Death 1 week later
	F, 53	Osteoarthritis; 200–400 mg/d, 6 months	Jaundice and dark urine	TB 18,ALP 2.6, ALT 29	Severe hepatic necrosis	TOH 1 month later
	F, 49	Osteoarthritis; 200 mg/d 6 months	Jaundice	TB 4.8, ALP 2.2, ALT 16	Necrosis	Cirrhosis after 19 months
Fok et al. 2013 [35]	F, 83	Osteoarthritis; 10 months	Asymptomatic	ALP 5, ALT 4.5	Ductal proliferation and ductopenia. Inflammatory portal infiltration with neutrophils, lymphocytes and occasional eosinophils and plasma cells.	Normalization

F: female; M: male; TB: total bilirubin; ALP: alkaline phosphatase; ALT: alanine-aminotransferase; LT: liver transplantation; UDCA: ursodeoxycholic acid; ARF: acute renal failure.

Table 3. Calculated risk of drug-induced liver injury with coxibs in different studies.

Drug	Study design	Study period	Sample size	Reported risk	Ref. Nº
Celecoxib	Prospective randomized, double-blind trial in patients with OA and RA (celecoxib *vs*. NSAIDs for 6 months)	1998–2000	3987 people	Serum ALT or AST elevations exceeded 3 times the ULN limit of normal: 0.6% *vs*. 2.3% ($p < 0.05$)	[36]
Celecoxib	Retrospective cohort and nested case–control study (nimesulide *vs*. other NSAIDs)	1997–2001	48,294 and 6619 people/year for nimesulide and celecoxib, respectively	Twice ULN for ALT or conjugated bilirubin, or a combined increase of AST, AP, and total bilirubin: 33.1 *vs*. 15.2 per 100,000 people/year	[37]
Celecoxib	Case/non-case analysis of spontaneous reports using FDA/FOI and WHO/UMC databases	Up to the end of quarter 1 and 3 of 2003 for FDA and WHO, respectively	12,499 and 16,599 reports for FDA and WHO, respectively	Overall hepatic disorders for FDA and WHO, respectively, OR 0.72 (IC95% 0.66–0.79) and 0.63 (IC95% 0.57–0.69)	[38]
Rofecoxib	Case/non-case analysis of spontaneous reports using FDA/FOI and WHO/UMC databases	Up to the end of quarter 1 and 3 of 2003 for FDA and WHO, respectively	17,748 and 20,429 reports for FDA and WHO, respectively	Overall hepatic disorders for FDA and WHO, respectively, OR 0.63 (IC95% 0.57–0.69) and 0.43 (IC95% 0.39–0.48)	[38]
Etoricoxib	Pre-specified pooled analysis of data from 3 prospective randomized, double-blind, clinical trials in patients with OA and RA (etoricoxib *vs*. diclofenac)	2002–2006	17,412 people	Discontinuation due to liver test abnormalities or other hepatic events: 0.3–0.4% *vs*. 1.5–5.0%	[39]

OA: osteoarthritis; RA: rheumatoid arthritis; ULN: upper limit of normal; AP: alkaline phosphatase; FDA/FOI: Food and Drug Administration/Freedom of Information; WHO/UMC: World Health Organization Uppsala Monitoring Centre.

and leaving in the last positions two COX-2 inhibitors, namely rofecoxib (cholestatic hepatitis) and etoricoxib (hepatocellular pattern) [45]. Finally, DILIN registry from the USA, which has currently recruited 899 patients, found coxib-induced liver damage to occur only in 4 of them, caused by either celecoxib ($n = 3$) and valdecoxib ($n = 1$) [46]. Diclofenac-induced hepatotoxicity leaded the list, with 12 patients in this registry (Table 4). However, it is important to highlight that etoricoxib is not marketed in the USA. In addition, the conclusions that can be drawn from comparing rates of NSAID-induced hepatotoxicity among the different registries could be limited by differences in the sample size and length of exposure, among other factors.

Table 4. NSAIDs-induced liver toxicity in three different registries: Spanish DILI registry [45], United States DILI Network [46], and Latin American DILI registry [45].

Individual agent (n)	Spanish DILI registry (1994–2015) (n = 867)≠	DILIN study (2004–2015) (n = 899)	Latin DILI registry (2011–2015) (n = 200)≠
Non-coxibs NSAIDs			
Diclofenac (41)	16	12*	13
Nimesulide (20)	9	-	11
Ibuprofen (30)	22	1	7
Meloxicam (5)	2	3	0
Etodolac (2)	0	2	0
Sulindac (1)	0	1	0
Ketorolac (3)	2	-	1
Total	51	19*	32
Coxibs (8)			
Celecoxib (3)	-	3	-
Rofecoxib (2)	1	-	-
Etoricoxib (2)	1	-	1
Valdecoxib (1)	-	1	-
Total	2	4	1

*Three more cases of diclofenac + misoprostol; ≠ Only cases with a single culprit drug. Etoricoxib is not marketed in the USA.

These despair findings between different registries might be due to differences in either pharmaceutical policies or prescription patterns among geographic areas. According to information of the Agencia Española de Medicamentos y Productos Sanitarios, NSAID consumption increased 26.5% throughout the 2000–2012 period. Ibuprofen was the first NSAID consumed, followed by diclofenac. The use of celecoxib and rofecoxib rose during the first year of the series, but dropped when, in 2004, rofecoxib was withdrawn from the market. From 2006 onwards, the consumption of celecoxib and etoricoxib (commercialized since 2005) increased, and in 2012, represented 14.7% of the total consumption of NSAIDs in Spain (Figure 2) [47]. It is noteworthy that nimesulide was withdrawn from the Spanish market in 2002, but in the years it was marketed, the drug had an average use of 0.586 defined daily dose (DDD) per 1000 inhabitants-days, a figure higher than that of aspirin (0.175 DDD per 1000 inhabitants-days) [47,48].

The average number of prescription of coxibs and NSAIDs per patient in the USA is shown in Figure 3 [49]. Nimesulide and etoricoxib have never been marketed in the USA and, unfortunately, there are not accessible detailed data about prescriptions of NSAIDs in Latin America. However, a well-designed prospective prescription-based study in the general population to analyze the real incidence of liver injury linked to these compounds has never been carried out.

4. The wide spectrum of liver damage induced by coxibs

4.1. Celecoxib

As stated above, and according to recent research, the hepatic compromise induced by coxibs is a rare event. In a long-term study evaluating the safety profile of celecoxib in arthritis

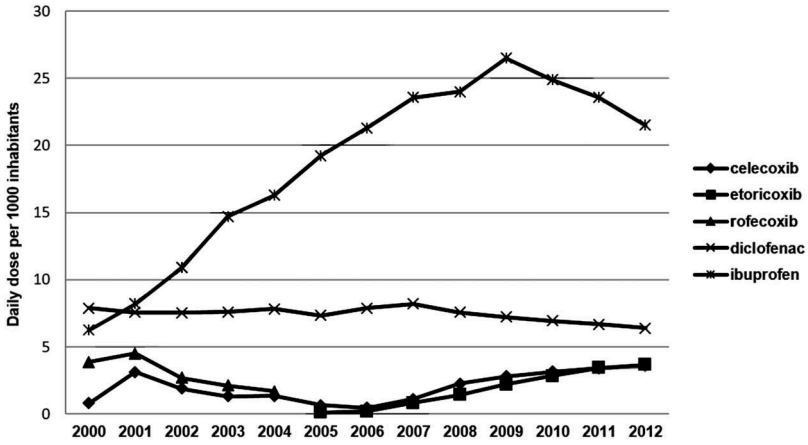

Figure 2. Evolution of ibuprofen, diclofenac, and selective COX-2 inhibitor consumption (daily dose per 1,000 inhabitants) in Spain, throughout the 2000–2012 period. Data taken from [47].

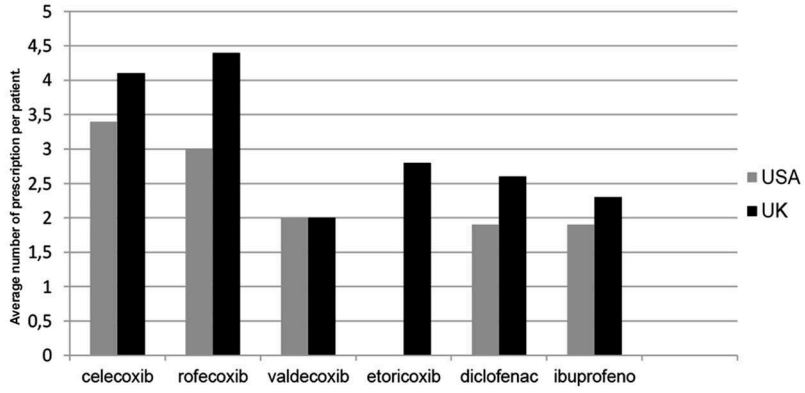

Figure 3. Average number of prescriptions per patient of NSAIDs and coxibs in USA and UK, throughout the 1995–2004 period. Figures are based on the PharMetrics data (43 million US patients from 73 health care plans). Data taken from [49].

subjects (CLASS (Celecoxib Long-term Arthritis Safety Study)), the authors observed increased transaminases in 0.6% of the cases, but only 0.2% of them showed ALT values >3 × ULN [36]. In spite of the existence of isolated reports of symptomatic cholestatic hepatitis induced by celecoxib [17–26], in a review of 14 controlled trials, Maddrey et al. [50] showed that the frequency of celecoxib-induced hepatic reactions was lower than that of other NSAIDs, and not significantly different from that of placebo group (0.8% *vs*. 0.9%, respectively). They also reported that symptom onset occurred between 4 days and 4 weeks after the first celecoxib intake, and five out of six reactions were in women. Biochemical liver tests were described as hepatocellular or mixed liver injury. Eosinophilia was only observed in a few cases.

Soni et al. [51] confirmed these results in their analysis of 41 randomized controlled trials. The incidence of hepatic adverse events and laboratory abnormalities in patients treated with celecoxib was similar to that in patients treated with placebo plus two conventional nonselective NSAIDs, ibuprofen and naproxen, but lower than that for diclofenac. Some limitations of this study should be however considered, such as the heterogeneous quality of the studies selected, difficulties in estimating the incidence of adverse events due to the low frequency of drug reactions, and the fact that acetaminophen was not included in the comparison. Nevertheless, the results are in line with the current guidance for no need for dosage adjustments in patients with mild hepatic damage, and prescription at the lowest recommended dose in patients with moderate one. The benefit-to-risk ratio associated with celecoxib remains therefore acceptable.

In contrast to these data, a Taiwanese study [40] showed an increased risk of hospitalization for acute hepatitis induced by celecoxib. They studied 4519 cases of hospitalization due to acute hepatitis, by using a unidirectional, case-crossover design. They observed a significant odds ratio for increased risk of liver damage of celecoxib, nimesulide, diclofenac, ibuprofen, and other hepatotoxic NSAIDs.

Although celecoxib has a low degree of hepatic adverse events, it must be prescribed with caution. The use of most COX-2 inhibitors seems to increase the risk of cardiovascular adverse events in a dose-related manner, and patients should be informed accordingly of this threat. Celecoxib should be only used at the lowest effective dose and for short time periods (weeks). It should be avoided in patients with cardiovascular disease or diabetes, or those at increased risk of cardiovascular events [52]. Therefore, assessment of the patient's baseline risk for cardiovascular disease (e.g. by using the Framingham's Coronary Heart Disease Risk Score) is highly recommended.

In line with these recommendations, The Agencia Española de Medicamentos y Productos Sanitarios launched a warning letter in February 2005 on the use of coxibs so as to improve its benefit to risk balance [53].

4.2. Lumiracoxib

An increase in the transaminase levels was associated with the administration of high doses of lumiracoxib (3%) [54]. Indeed, this study carried out in the USA shows a higher frequency of clinical hepatitis among patients receiving lumiracoxib, as compared to those receiving ibuprofen and naproxen. These results were corroborated by a research group from the UK, which documented that lumiracoxib is associated with a clinical and biochemical pattern of severe hepatocellular damage; this situation prompted the health authorities in these countries to permanently withdraw the drug from the market [14]. The Scottish Ministry of Health has reported 20 cases of serious acute hepatitis due to lumiracoxib until 2007, with the development of acute liver failure in 14 of them (two patients died due to multiorgan failure, and 3 of them required liver transplantation) [15]. In line with these data, post-marketing reports from Australia have also shown that lumiracoxib was associated with acute liver failure (2 patients died, and 2 required liver transplantation, from a total of 8 cases). This serious situation also forced health authorities from that country to permanently withdraw lumiracoxib from the market [16]. Description of the liver damage phenotype and outcome related to lumiracoxib is depicted in Table 2 [34,35].

A genome-wide association study (GWAS) conducted on subjects on lumiracoxib treatment with and without liver damage has shown a significant association with hepatic damage in patients with the SNP rs9270986 in the human leukocyte antigen (HLA) region [55]. A more detailed mapping has identified a strong association with the haplotype HLA-DRB1*15:01-DQB1*06:02-DRB5*01:01-DQA1*01:02, with HLA-DRB1*15:01 being the most significant allele (OR 5, 95% CI 3.6–7). An essential goal of pharmacogenomics is the genotyping of users before drug prescription in order to identify those individual at high risk of presenting an adverse reaction. Applying the data presented by Singer et al. [55], the prospective genotyping for HLA DQA1*01:02 would reduce the incidence of hepatotoxicity due to lumiracoxib from 5.6% to 1.0% in noncarriers for this mutation [56].

4.3. Rofecoxib

Opposite to lumiracoxib, rofecoxib has been shown to present a low rate of hepatic events in several studies. An increase in the serum levels of ALT (≥3 × ULN) was observed only in 1.8 per 100,000 exposed persons per year [12]. However, Yan et al. [33] reported two very well-documented cases of cholestatic hepatitis induced by rofecoxib. Both patients differed in liver test profile; one of them showed high serum levels of alkaline phosphatase (ALP), associated with marked periportal necrosis (zone 1) on histological examination, whereas the other one showed a marked increase in ALT serum levels, with minimal abnormality in ALP levels. In the histology, only mild damage in zones 1 and 3 of the liver acinus was apparent.

In addition to this report, other 6 rofecoxib-induced hepatotoxicity cases have been reported, all of them with a predominantly cholestatic clinical presentation. Liver test normalization was achieved within 6 months after drug withdrawal in all patients. Ursodeoxycholic acid therapy was administered due to intense cholestasis in 4 of them, and steroids treatment was indicated in 1 patient. The main indication for rofecoxib treatment was osteoarthritis and arthralgia [27–33].

4.4. Valdecoxib

According to literature, valdecoxib seems to have a good hepatic safety profile. In a systematic review including 65 randomized clinical studies, patients with osteoarthrosis who received ibuprofen, naproxen, meloxicam, celecoxib, and valdecoxib treatment during a maximum period of 4 weeks showed similar values of transaminase elevations to that of the placebo group. On the other hand, in the same study, diclofenac and rofecoxib showed ALT levels higher than the remaining NSAIDs [42]. Despite there is only one case of valdecoxib-induced liver injury included in DILIN Registry [46], we were unable to find any published case of both asymptomatic and/or jaundiced liver injury associated with valdecoxib in the literature. Finally, valdecoxib was withdrawn from the market due to serious dermatological and cardiovascular reactions [8].

4.5. Etoricoxib

We could not retrieve any report of acute liver damage induced by etoricoxib in the literature. However, an asymptomatic increase in ALT and/or AST (≥3 × ULN) has been reported in approximately 1% of the cases using this drug for at least 1 year [57,58]. This drug has not been approved in the USA. It has been extensively studied in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program, a double-blind randomized comparison of diclofenac (150 mg) and etoricoxib (60–90 mg) in patients with osteoarthritis and rheumatoid arthritis, designed to assess associated thrombotic cardiovascular events [39]. Laine et al. [59] reported liver-related events in more than 34,000 patients enrolled in the MEDAL program. This study showed increments in ALT or AST levels (≥3 × ULN) in 3.1% of the patients taking diclofenac and in 0.7% of those treated with etoricoxib. When analyzing the rate for drug discontinuation due to hepatic reactions, the authors observed that those receiving diclofenac had significantly higher percentage of dropouts as compared with the group treated with etoricoxib (2.7% *vs*. 0.3%, respectively). The hospitalization rate due to hepatic adverse events was low in both groups (0.02% *vs*. 0, respectively). No cases associated with acute liver failure, liver transplantation, or treatment-related deaths was reported. However, due to the infrequency of clinically apparent hepatotoxicity, cohort studies in patients under treatment with the drug of interest were generally unpowered, and failed to detect clinical events.

5. Old and new hypothetical mechanism of liver damage

5.1. General mechanism of coxib-induced hepatotoxicity

The mechanisms of coxib-induced liver damage have not been fully elucidated. Probably, the COX-2 inhibition, which is the main pharmacological mechanism of action, may play a role; however, since other NSAIDs also have COX-2 inhibitory activity, this mechanism alone cannot explain susceptibility to a specific coxib, but could be a contributing factor. Although controversial, COX-2 has been regarded as a hepatoprotective enzyme that is induced in liver upon necroinflammation induced by hepatotoxicants, as has been shown in murine models of thioacetamide and CCl_4-induced hepatotoxicity, and in liver fibrosis induced by a choline-deficient diet [60–62]. Furthermore, COX-2-derived mediators such as prostaglandin E_2 (PGE_2) have an important hepatoprotective role in acetaminophen-induced hepatotoxicity in mice [63]. Hepatoprotective effects of PGE_2 includes: (1) stimulation of signal transduction pathways involved in liver regeneration, by acting as endogenous ligands in these pathways [60,64,65], and (2) anti-inflammatory effects, by upregulation of anti-inflammatory cytokines [66–70]. Apart from PGE_2, COX-2 also produces the PGD2 metabolite 15-deoxy-delta(12,14)-PGJ2, which is also a potent anti-inflammatory molecule that inhibits the production of the proinflammatory cytokines TNF-α and IL-1ß by human macrophages [66]. Stimulated prostaglandin (PG) synthesis in transgenic mice that express human COX-2 in hepatocytes decreases the liver injury induced by galactosamine/lipopolysaccharide or concanavalin A administration, two models of acute hepatitis, and this effect was suppressed by COX-2-selective inhibitors [71]. Finally, inhibition of PG synthesis by coxibs downregulates Bcl-2, an anti-apoptotic mitochondrial protein that protects against bile acid-induced apoptosis [72].

All these findings prompted the authors to propose that COX-2 inhibition by coxibs may lead to loss of the protective mechanisms that normally follow COX-2 induction, making the liver susceptible to progression of injury. This mechanism of injury, yet plausible in an experimental model of acetaminophen-induced acute liver injury in mice [63], remains however controversial. Further experimental and clinical data suggested that increased COX-2 expression and PG production might contribute rather than attenuate liver damage, since PGs can elicit either pro- or anti-inflammatory effects depending on the nature of the inflammatory stimulus [73]. Whether this latter beneficial effect of coxibs reflects interference with deleterious metabolic pathways of these hepatotoxicants in particular that overcomes putative detrimental effects of coxibs or whether they represent a still uncharacterized, more general mechanism of hepatoprotection by coxibs that explains its lower toxicity remains to be ascertained. The fact that coxibs inhibit COX-2 but not COX-1, a constitutive isoform of COX which continuously synthesizes prostanoids and downstream PGE_2, may also contribute to explain their reduced toxicity, as compared with nonselective COX-2 inhibitors. A recent study revealed a protective role for COX-1 in liver injury induced by carbon tetrachloride, including attenuation of oxidative stress, inflammatory response, and apoptosis through both intrinsic and extrinsic apoptotic pathways [74], suggesting that COX-1 may have a hepatoprotective function by reassuring a basal production of hepatoprotective PGs via PGE_2 COX-1.

Apart from the general mechanisms of toxicity that coxibs may have by inhibiting PG synthesis together with other NSAIDs, each coxib have particular chemical and structural properties and metabolic pathways that contribute to explain its specific hepatotoxic potential.

Lumiracoxib, which has been removed from the market because of severe hepatotoxicity, is the only member of the coxib family structurally related to diclofenac, a drug well known to cause drug-induced liver injury. In lumiracoxib, the phenylacetic acid has a methyl group in meta position, and one of the two chlorines of the aniline ring system has been replaced by fluorine (see Figure 1). Like diclofenac, lumiracoxib can form reactive metabolites and adducts with glutathione; the latter even can deplete glutathione, and induce covalent binding to proteins and oxidative stress [75]. Kang et al. [76] and Li et al. [75] suggested that microsomal bioactivation of lumiracoxib to a quinone imine that is trapped by N-acetylcysteine (NAC) to form two NAC adducts, as well as bioactivation of its main metabolite 4′-hydroxylumiracoxib (M5) by several peroxidases and cytochrome P450 to form mono-, di-, tri-, and tetra-GSH adducts, may both be responsible for these deleterious effects. Interestingly, patients who are carriers of the *ABCB11* 1331CC polymorphism, which is associated with low activity of the bile salt export pump (BSEP), and that received NSAIDs bearing chemical moieties with known BSEP inhibiting effects (e.g. carbocyclic system with at least one aromatic ring), have higher risk of developing DILI [77].

Detectable titers of serum autoantibodies, mostly antinuclear antibodies, were present in three cases of lumiracoxib-induced hepatotoxicity [34], suggesting the occurrence of immune-mediated mechanism in the pathogenesis of coxib-induced DILI.

5.2. Genetic susceptibility

There are few works studding the pharmacogenomic behavior of COX-2 inhibitors, but genetic susceptibility has been proved for certain coxibs (Table 5).

The possibility that genetic variations in host immunity have a critical role is supported by a genome-wide association study carried out in 41 cases of lumiracoxib-induced DILI and 176 drug-tolerant lumiracoxib-exposed patients, as controls [55]. A strong association between lumiracoxib-induced hepatotoxicity and specific HLA markers within the major histocompatibility complex class II region was found. From the many HLA alleles identified, HLA-DQA1*0102 was the most sensitive (73.6%) in predicting risk [80]. As mentioned above, lumiracoxib can produce reactive metabolites able to generate antigenic drug–protein adducts, which could be presented at the cell membrane by HLA complexes, and trigger a T cell-mediated immune response. Alternatively, lumiracoxib could

Table 5. Genetic variations potentially relevant to coxib-induced liver injury.

Causative drug		Ref.
Association of HLA genotypes with coxib-induced liver injury		
Lumiracoxib	*DRB1*1501*; OR 7.5 (95% IC 5.0–11.3) *DQB1*0602*; OR 6.9 (95% IC 4.6–10.3) *DRB5*0101*; OR 7.2 (95% IC 4.8–10.8) *DQA1*0102*; OR 6.3 (95% IC 4.1–9.6)	[55]
Association of metabolizing enzyme polymorphisms with coxib-induced liver injury		
Celecoxib	CYP2C9; decreased clearance in carriers of the Ile359Leu (*3) variant, particularly homozygous	[78]
Rofecoxib	UG2B7and UG2B15; different catalytic efficiency for the glucuronidation of 5-hydroxyrofecoxibin human liver microsomes	[79]

interact directly with the HLA complex to prompt an immune response.

A possible role for polymorphisms in human UDP-glucuronosyltransferase (UGT) isoforms responsible for rofecoxib metabolism (UG2B7 and UG2B15) has also been proposed [79]. This is somewhat expected, since glucuronidation by these UGT isoforms of derivatives of cytochrome P450-mediated metabolites are one of the detoxification pathways of rofecoxib, allowing both biliary and renal excretion of the glucuronidated forms [81].

As many others drugs, celecoxib is metabolized in the liver by cytochrome P450 isoforms, mainly CYP2C9, and the hypothesis of abnormal high serum levels of celecoxib appear in poor metabolizers of CYP2C9 substrates, as shown by Prieto et al. [78]. They analyzed the pharmacokinetic parameters of celecoxib, according to CYP2C9 genotype in 24 subjects, and they found a clearance reduced by half in heterozygous subjects and by 10-folds in homozygous in allele *3 carriers, as compared with wild-type carriers.

Although prediction of NSAID hepatotoxicity in a given individual is currently unfeasible, a better understanding of how genetic predisposition interacts with other host factors, along with the development of diagnostic and prognostic biomarkers, would help the application of precision medicine in this field.

6. Expert opinion

Most coxibs (rofecoxib, valdecoxib, parecoxib, and lumiracoxib) were withdrawn from the market due to serious cardiovascular, dermatological, and hepatic reactions. In particular, lumiracoxib induced cases of severe hepatitis and acute liver failure, being the only coxib permanently withdrawn from the market due to hepatotoxicity.

Celecoxib and etoricoxib are currently the only marketed coxibs, and they have been scarcely related to hepatotoxicity, as was previously highlighted in this review. With celecoxib, there have been published isolated reports of cholestatic hepatitis, while for etoricoxib, most of the data showed that the drug is related to asymptomatic hypertransaminasemia.

From our extensive revision of the literature, we were not been able to document the exact incidence of hepatotoxicity, due to the fact that the cohort studies carried out so far were generally unpowered to detect this rare clinical event.

Regarding the mechanisms of liver damage, and apart from the general mechanisms of toxicity that coxibs may have by inhibiting PG synthesis together with other NSAIDs, each coxib have particular chemical and structural properties and metabolic pathways that may contribute to explain its specific hepatotoxic potential. The exact underlying mechanisms of coxibs-induced hepatotoxicity remain uncertain. COX-2 is tentatively regarded as hepatoprotective by producing anti-inflammatory/antiapoptotic PGs, and this putative beneficial effect is expected to be impaired by coxibs; however, unbeneficial rather than protective roles for COX-2 in certain cases of drug-induced liver injury have challenged this concept. A possible role for several polymorphisms, such as HLA complex, and certain cytochrome P450 and UGT isoforms, can also explain individual susceptibility to coxibs-induced liver damage. Despite these findings, none of these polymorphisms are still used for routine evaluation in patients suspected to have coxib-induced liver damage.

An unresolved question is the relationship between a previous sulfonamide allergy and celecoxib-induced liver toxicity. Current manufacturer recommendations are to avoid celecoxib in people with clearly documented sulfonamide allergy, because reports of cross-reactivity and toxicity have been published [82]. Although celecoxib does contain a sulfonamide moiety, others have pointed out that the critical N1- or arylamine substituents (associated with sulfonamide antimicrobial hypersensitivity) are absent [83,84].

Although the hepatic safety profile of coxibs, like its gastrointestinal safety profile, could be more favorable than those of nonselective NSAIDs, a well-designed prospective prescription-based study in general population to analyze the real incidence of liver injury linked to these compounds has not been carried out so far. Hence, physicians should be aware of the possibility of hepatotoxicity when prescribing these drugs. Despite coxibs have a low potential for hepatotoxicity, the patient should ask for medical advice if abdominal pain, vomiting, dark urine or jaundice, either with or without pruritus, appears.

Meanwhile, post-marketing surveillance policies from regulatory agencies will be an invaluable tool to establish the actual benefit-to-risk balance of coxibs.

The selection of which NSAID should be prescribed in clinical practice should be provided by consensus/guidelines. Prescription of a particular coxib will be very much dependent on the patient's clinical condition, which is mainly associated with risk factors for gastrointestinal bleeding.

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