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Identification of NSAID Users at Risk for Gastrointestinal Complications

A Systematic Review of Current Guidelines and Consensus Agreements

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Contents

Abstract

NSAIDs are among the most often used drugs worldwide. Numerous NSAID users are at risk for developing gastrointestinal complications. The purpose of this review was to identify and stratify risk factors for gastrointestinal complications in NSAID users documented in guidelines and consensus agreements, and to collect recommendations regarding over-the-counter (OTC) NSAID use. To facilitate this, a PubMed search from 1 January 1999 until 1 March 2009 was performed, resulting in the inclusion of nine English-language guidelines in our analysis. Risk factors were defined as 'definite' if mentioned in all guidelines; otherwise they were defined as 'controversial' risk factors.

'Definite' risk factors were a history of (complicated) peptic ulcer disease, older age (cut-off range 60–75 years), concomitant anticoagulant or corticosteroid use and multiple NSAID use, including low-dose aspirin

(acetylsalicylic acid). 'Controversial' risk factors were high-dose NSAID use, concomitant clopidogrel or selective serotonin reuptake inhibitor use, a history of gastrointestinal symptoms, rheumatoid arthritis disability and cardiovascular disease. Infection with *Helicobacter pylori* was identified as an additive risk factor. Risk factors in OTC NSAID users were difficult to identify in the current literature.

Risk factors were not all uniformly present in analysed guidelines and consensus agreements. We identified a history of (complicated) peptic ulcer disease, older age, concomitant anticoagulant or corticosteroid use and multiple NSAID use, including low-dose aspirin, as definite gastrointestinal risk factors in NSAID users.

NSAIDs are amongst the most frequently prescribed drugs, but their use can be aggravated by adverse effects.[1-4] The most commonly reported adverse effects are gastrointestinal, cardiovascular and renal complications. Gastrointestinal adverse effects range from gastrointestinal complaints without visible mucosal lesions at endoscopy to serious gastrointestinal bleeding.[4] The prevalence of upper gastrointestinal complaints varies between 5% and 50% of patients receiving traditional and cyclooxygenase (COX)-2 selective NSAIDs.[5-8] Common symptoms are epigastric pain, heartburn, nausea, regurgitation, bloating and diarrhoea.[9] About 1–2% of NSAID users require admission to a hospital for serious complications, such as gastric perforation and bleeding, both of which are associated with a high mortality rate.[10,11]

A frequently employed method to minimize gastrointestinal risk associated with NSAID use is co-prescription of a gastroprotective agent, such as a proton pump inhibitor (PPI) or misoprostol.[12-20] This strategy, however, is only cost-effective in NSAID users at high gastrointestinal risk.[21] Therefore, several guidelines and consensus agreements were published that designate patients at risk for gastrointestinal complications.[12-20] This distinction is based on patient-related risk factors. Guidelines and consensus agreements are not uniform in discussing risk factors or in otherwise attributing the importance of risk factors. Some risk factors are undisputed by authors of analysed guidelines and consensus agreements whereas others are considered more controversial.

Another issue of concern is gastrointestinal risk in the growing population of over-the-counter (OTC) NSAID users.[13] OTC NSAID use is often propagated by general physicians and specialists, but is seldom adequately monitored. A questionnaire-based study performed in Italy by Motola et al.[22] showed that 23% of 2738 randomly selected subjects had used NSAIDs in the previous week, of which 44% were bought OTC. No gastrointestinal complication prevention studies in OTC users have yet been reported. As a consequence, evidence-based guidelines do not recognize the potential gastrointestinal risk in OTC NSAID users. The growing OTC consumption of NSAIDs could well contribute to the incidence of gastrointestinal adverse effects and therefore should be addressed.

The aim of this study is to systematically review guidelines and consensus agreements identifying NSAID users, including those prescribed NSAIDs and those obtaining NSAIDs OTC, who are at risk of gastrointestinal events. The emphasis of this review will be on individual risk factors for gastrointestinal adverse effects, the role of OTC availability and the recognition of these in guidelines and consensus agreements.

1. Literature Search

We conducted a structured search in PubMed to identify English-language clinical guidelines or consensus agreements regarding risk management of gastrointestinal adverse events in NSAID users, with an emphasis on risk factors and OTC use. Publications from 1 January 1999

until 1 March 2009 were included. If a group of authors published more than one guideline, only the most recent was included.

In the search strategy, the following subject headings and keywords were used: 'anti-inflammatory agents, non-steroidal' [MeSH] or 'nonsteroidal anti-inflammatory drugs' or 'NSAID' and 'guideline' or 'consensus'. The following limits within PubMed were used: published in the last 10 years, humans, meta-analysis, practice guideline, consensus development conference. The reviewers (MT and TE) then individually assessed the relevancy of all abstracts corresponding with the remaining titles, and excluded abstracts for the following reasons: (i) not concerning gastrointestinal risk factors during NSAID use; (ii) not written in English; and (iii) no guideline or consensus agreement. From selected abstracts, full papers were reviewed and were only rejected if they (i) made no reference to gastrointestinal risk factors, or (ii) were neither guidelines nor consensus agreements. Remaining manuscripts were independently assessed by the reviewers and included if they contained information regarding consideration of gastrointestinal risk factors in the management of NSAID users. Disagreements were adjudicated by discussion and consensus between the two primary reviewers and a third-party arbiter (MvO).

1.1 Outcomes

Our main interest was to identify common gastrointestinal risk factors among included guidelines and consensus agreements. For this purpose, we conducted a summary table for proper overview of all stated risk factors. Risk factors present among all included guidelines were defined as 'definite' risk factors. Remaining factors were discussed as 'controversial' risk factors. Classification, as indicated by the authors, of guidelines included was adopted.

OTC use was often not fully incorporated in guidelines; therefore, all statements regarding OTC NSAIDs were collected and presented in a separate table.

2. Findings

A total number of 224 studies were found, of which 215 articles were excluded in two selection procedures. The main reason for exclusion was no mention of a guideline or consensus agreement (figure 1). Two articles were not written in English; the remaining nine guidelines were scrutinized by systematic review. Characteristics of included studies are shown in table I.

2.1 Definite Risk Factors

Risk factors for gastrointestinal complications in NSAID users present in all analysed guidelines could be defined as 'definite' risk factors. We defined the following risk factors as 'definite': history of complicated (defined as peptic ulcer bleeding, obstruction or perforation) and uncomplicated peptic ulcer disease, older age, concomitant anticoagulant use, concomitant corticosteroid use and concomitant low-dose aspirin (acetylsalicylic acid) or multiple NSAID

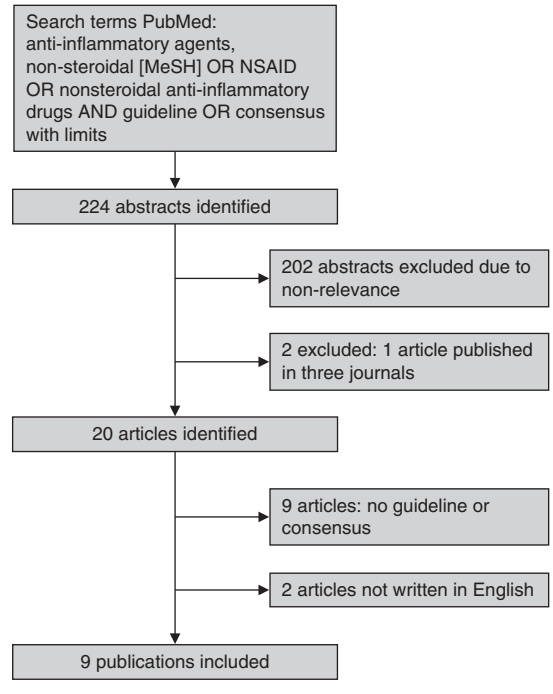

Fig. 1. Results of the literature search.

Table I. Studies included in the review

Study (y)	Specialization	Country
Lanza et al.[16] (2009)	Gastroenterology	USA, Hong Kong, Ireland
Bhatt et al.[13] (2008)	Cardiology, gastroenterology	USA
Chan et al.[14] (2008)	Gastroenterology	Hong Kong, USA
Rostom et al.[17] (2009)	Gastroenterology	Canada
American College of Rheumatology[12] (2008)	Rheumatology	USA
Targownik and Thomson[19] (2006)	Gastroenterology, family medicine	Canada
Wilcox et al.[20] (2006)	Gastroenterology, rheumatology, cardiology, internal medicine	Canada, USA, Spain
Dubois et al.[15] (2004)	Medical researcher	USA
Schoenfeld et al.[18] (1999)	Gastroenterology	USA

use (figure 2, and tables II and III). In this review we report on the most discussed variables only – older age and the use of multiple NSAIDs.

2.1.1 Older Age

All included studies regarded older age as definite risk factor, but the exact threshold was not uniform and ranged from 60 to 75 years. Bhatt et al.,[13] Rostom et al.[17] and Schoenfeld et al.[18] considered patients to be at high risk if they were aged >60 years. Age >65 years was considered a risk factor by Lanza et al.[16] and Dubois et al.[15] Significant increased risk for gastrointestinal complications in patients aged >70 years was described by Chan et al.[14] The threshold in the guidelines of the American College of Rheumatology[12] was 75 years, which is similar to the guideline by Targownik and Thomson,[19] i.e. 76 years and older. Wilcox et al.[20] did not dichotomize risk stratification according to an age threshold; they stated that advancing age increases gastrointestinal risk by about 4% per year.

2.1.2 Multiple NSAIDs and Concomitant Low-Dose Aspirin (Acetylsalicylic Acid)

Intake of more than one type of NSAID was regarded as a risk factor in most guidelines and consensus articles. Some consensus groups considered low-dose aspirin (75–325 mg daily) as a separate risk factor,[12-17,19] while others regarded low-dose aspirin as a (sub)type of traditional NSAIDs.[18,20] Higher gastrointestinal risk by use of multiple NSAIDs, including concomitant

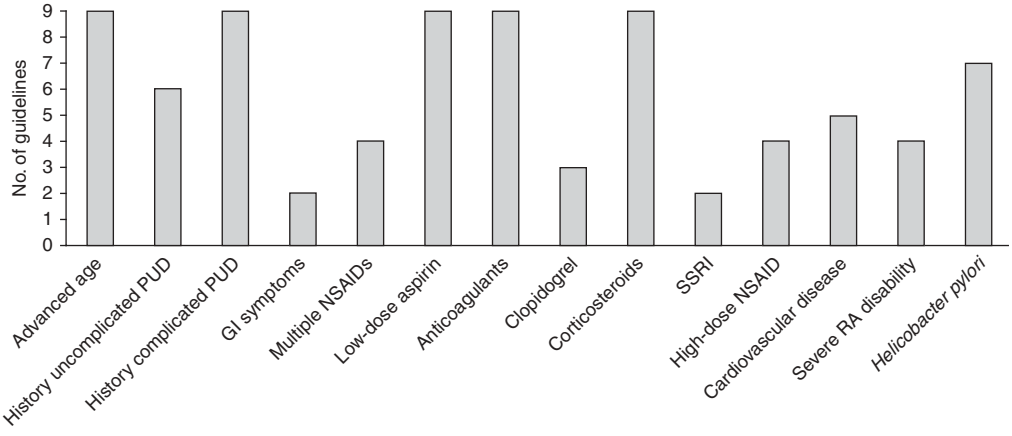

Fig. 2. Presence of risk factors in analysed guidelines and consensus agreements. **GI** = gastrointestinal; **PUD** = peptic ulcer disease; **RA** = rheumatoid arthritis; **SSRI** = selective serotonin reuptake inhibitor.

Table II. Overview presence of risk factors in analysed guidelines

Risk factor[a]	Lanza et al.[16]	Bhatt et al.[13]	Chan et al.[14]	Rostom et al.[17]	Am Col Rheum[12]	Targownik and Thomson[19]	Wilcox et al.[20]	Dubois et al.[15]	Schoenfeld et al.[18]
Age (y)									
Age; threshold	Δ >65	Δ ≥60	Δ ≥70	Δ >60–75	Δ >75	Δ ≥76	Δ[b]	▲ ≥65	▲ ≥60
History									
Complicated PUD	▲	▲	Δ	Δ	Δ	Δ	▲	▲	▲
Uncomplicated PUD	Δ	▲	NP	Δ	NP	Δ	▲	Δ	NP
GI symptoms	NP	Δ	NP	Δ	NP	NP	NP	NP	NP
Concomitant therapy									
Multiple NSAIDs[c]	NP	Δ	NP	Δ	NP	NP	Δ	NP	Δ
Low-dose aspirin (acetylsalicylic acid)	Δ	Δ	Δ	Δ	Δ	Δ	[d]	▲	[d]
Anticoagulant	Δ	▲	Δ	Δ	Δ	Δ	Δ	Δ	▲
Clopidogrel	NP	▲	Δ	Δ	NP	NP	NP	NP	NP
Corticosteroids	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ
SSRI	NP	NP	NP	Δ	NP	Δ	NP	NP	NP
Dosage									
High-dose NSAID	Δ	NP	NP	Δ	NP	NP	Δ	NP	Δ
Co-morbidity									
Cardiovascular disease	Δ	NP	NP	Δ	Δ	NP	[e]	NP	Δ
Severe RA disability	NP	NP	NP	Δ	Δ	NP	[e]	NP	Δ
Additive									
Helicobacter pylori	Δ	Δ	NP	Δ	Δ	Δ	Δ	NP	Δ

a If authors distinguished between moderate and high risk factors, moderate risk is indicated as Δ and high risk as ▲. If no distinction is made, all risk factors are indicated as Δ.

b Risk increases linear with 4% per advancing year.

c Including aspirin and cyclooxygenase-2 inhibitors.

d Low-dose aspirin was regarded as a NSAID.

e Co-morbidity in general was considered a risk factor.

Am Col Rheum = American College of Rheumatology; **GI** = gastrointestinal; **NP** = not present; **PUD** = peptic ulcer disease; **RA** = rheumatoid arthritis; **SSRI** = selective serotonin reuptake inhibitor.

low-dose aspirin, was considered a definite risk factor among all guidelines.

2.2 Controversial Risk Factors

The guidelines assessed for this systematic review were not uniform for all risk factors. No agreement was present for a history of gastrointestinal symptoms, high-dose NSAID use, concomitant clopidogrel therapy, concomitant selective serotonin reuptake inhibitor (SSRI) use and co-morbidity.

2.2.1 History of Gastrointestinal Symptoms

Only two guidelines considered the history of gastrointestinal symptoms as a risk factor for patients receiving NSAID therapy.[13,17] Upper gastrointestinal symptoms, described as upper abdominal pain or discomfort or increase of symptoms of gastroesophageal reflux disease, should be analysed according to the method of Bhatt et al.[13] and Rostom et al.[17] because, according to these authors, a positive history augments the relative risk for gastrointestinal complications.

2.2.2 High-Dose NSAID

In many, but not all, analysed guidelines, a high dose of NSAIDs is a risk factor for gastrointestinal complications;[16-18,20] however, the exact definition of high dose was not stated.

Table III. Risk factors identified in the guidelines

Definite[a]
Advanced age
History of (un)complicated PUD
Anticoagulants
Corticosteroids
Low-dose aspirin
Multiple NSAIDs
Controversial[b]
High-dose NSAID
Clopidogrel
SSRI
History of gastrointestinal symptoms
Rheumatoid arthritis disability
Cardiovascular disease
Additive[c]
Helicobacter pylori infection

a Definite risk factor is present in all analysed guidelines and consensus agreements.

b Controversial risk factor is not present in all guidelines.

c Additive risk factor is only of importance in patients with a history of peptic ulcer disease.

PUD = peptic ulcer disease; **SSRI** = selective serotonin reuptake inhibitor.

2.2.3 Concomitant Medication

Concomitant use of several drugs was regarded as a risk factor. As stated in section 2.1, corticosteroid, anticoagulant and low-dose aspirin use are definite risk factors. In all analysed guidelines, the use of clopidogrel and/or SSRIs was not considered to be a risk factor. Concomitant clopidogrel therapy was regarded as a risk factor in three of nine guidelines,[13,14,17] and concomitant SSRI use was mentioned in two guidelines.[17,19] Clopidogrel was approved in 1998 and since then the number of prescriptions has increased. Concomitant clopidogrel therapy has been recognized as a risk factor in the guidelines of Bhatt et al.,[13] Chan et al.[14] (published in 2008) and Rostom et al.[17] (published in 2009). However, the guideline published in 2009 by Lanza et al.[16] did not assess clopidogrel as a risk factor. Concomitant use of SSRIs is mentioned in two guidelines, namely in the guidelines of Rostom et al.,[17] and Targownik and Thomson.[19] The latter stated that the evidence of an increased number of complications is weak.

2.2.4 Co-Morbidity

The presence of rheumatoid arthritis or cardiovascular disease was included as a risk factor in several guidelines and consensus agreements. Severe rheumatoid arthritis was assessed as a risk factor in three guidelines (Rostom et al.,[17] American College of Rheumatology[12] and Schoenfeld et al.[18]). According to Schoenfeld et al.,[18] rheumatoid arthritis patients are more prone to use multiple and higher dosages of medications. Cardiovascular disease has been described by the same three groups[12,17,18] as being a risk factor for gastrointestinal complications. Schoenfeld et al.[18] defined cardiovascular disease as 'a history of heart disease'. The two other guidelines did not define cardiovascular disease. The clinical consequence of rheumatoid arthritis and cardiovascular disease in patients requiring NSAIDs appears to be independent of the background of the authors.

2.3 Additive Risk Factor

2.3.1 Helicobacter pylori

Infection with *Helicobacter pylori* is a known risk factor for peptic ulcer disease,[23] but the exact role of *H. pylori* in NSAID-related gastrointestinal complications is not yet clear.[23-25] Guidelines agree that patients with a history of (complicated) peptic ulcer disease who start NSAID therapy should be tested and treated for *H. pylori*; however, according to Lanza et al.,[16] eradication of *H. pylori* for secondary prevention of peptic ulcer bleeding alone seems insufficient in long-term NSAID users. This is mainly based on a large, randomized, double-blind clinical trial in *H. pylori*-positive naproxen users that showed statistically significant more recurrent upper gastrointestinal bleeding in patients treated with *H. pylori* eradication therapy compared with patients receiving long-term omeprazole (hazard ratio 7.1; 95% CI 1.9, 27.6).[24]

2.4 Over-the-Counter Use

One of the purposes of this systematic review was to identify recommendations regarding OTC NSAID use. OTC use has been increasing over the last decennia and is becoming more important;

however, we found little information about OTC NSAID use in the studied guidelines and consensus agreements. In particular, no information regarding identification of patients at risk for gastrointestinal side effects in OTC users was mentioned. Examples of statements from the literature regarding OTC NSAID use are provided in table IV.

3. Discussion

We found advanced age, history of complicated as well as uncomplicated peptic ulcer disease, concomitant use of multiple NSAIDs (including low-dose aspirin), concomitant use of anticoagulant therapy and concomitant use of corticosteroids to be definite risk factors for a gastrointestinal event in NSAID users. Controversial risk factors were concomitant use of clopidogrel and concomitant SSRI use, comorbidity, a history of gastrointestinal symptoms and high-dose NSAID use. Infection with *H. pylori* was regarded as an additive risk factor, which was only of importance in patients with a history of (un)complicated peptic ulcer disease.

Although older age was an undisputed risk factor throughout all included guidelines, the exact threshold remains under discussion. In our review, the threshold ranged from 60 to 75 years of age. One guideline noted a linear risk increase of 4% per advancing year.[20] The choice of an adequate threshold might be influenced by the patient population that the guideline refers to, but we could not identify specific thresholds within medical specializations and therefore attempted to determine other reasons for the wide range of this threshold. Many articles have been published about the cut-off value for advanced age in NSAID users; however, not all of these were cited in the different guidelines. For example, only two references that determine this cut-off age were used in more than one guideline.[26,27] We did not have insights into the reference selection procedures of the included guidelines, therefore the exact reasoning behind the chosen threshold remains unknown.

If medical costs are taken into account, coprescription of a gastroprotective agent or prescription of a selective COX-2 inhibitor is cost effective in patients older than 75 years and in patients with a history of (complicated) peptic ulcer disease, independent of their age.[21] Logically, costs are lower when the cheapest PPI is prescribed. No therapeutic strategy is currently cost effective in patients without risk factors.[21]

Concomitant use of multiple NSAIDs, including low-dose aspirin, was also defined as a definite risk factor. Gastrointestinal adverse effects of low-dose aspirin (75–325 mg/day) are mainly attributed to systemic side effects,

Table IV. Quotes on over-the-counter (OTC) NSAID use

Study	Statement
Lanza et al.[16]	"It is important to emphasize that physicians are often unaware that patients are self-medicating with low-dose aspirin when they are prescribed a NSAID for pain relief or anti-inflammatory effect."
Bhatt et al.[13]	"These agents, both through prescription and over-the-counter (OTC) use, are the most widely used class of medications in the United States."
	"As the incidence of arthritis complaints increases, the use of prescription and OTC NSAIDs is also expected to increase."
	"Recommendation: As the use of any NSAID, including COX-2-selective agents and OTC doses of traditional NSAIDs, in conjunction with cardiac-dose aspirin, substantially increases the risk of ulcer complications, a gastroprotective therapy should be prescribed for at-risk patients."
Rostom et al.[17]	"Nonsteroidal anti-inflammatory drugs are prescribed short term to about 25% of Canadians and long term (defined in this study as ≥6 months) to about 4%. However, this underestimates the magnitude of NSAID use as it does not include over-the-counter NSAIDs and low-dose aspirin is extensively used for cardiovascular risk reduction."
Wilcox et al.[20]	"Notably, both NSAID-associated gastrointestinal complications and deaths have been decreasing in recent years, after peaking in 1992. This decrease has been attributed to many factors including the use of lower-dose (particularly over-the-counter) NSAIDs, the decreasing prevalence … ."
Dubois et al.[15]	"In the year 2000 US patients received 111 400 000 prescriptions for non-steroidal anti-inflammatory drugs (NSAIDs), at a cost of nearly $5 billion, with an additional $2 billion spent on over-the-counter NSAIDs."
Schoenfeld et al.[18]	"In 1991, the year that naproxen and ketoprofen became available without prescription, an estimated 14 million Americans ingested NSAIDs on a daily basis."

whereas in high-dose NSAID users local gastric injury is also present.[28] However, several authors defined low-dose aspirin to be a traditional NSAID and therefore categorize it as multiple NSAID use.[18,20] Data are not uniform regarding the risks of solitary NSAID use and the combination of NSAIDs with low-dose aspirin. Relative risk estimations vary, from a 2-fold increase for solely low-dose aspirin use[29-31] to a 6-fold increase when combining NSAIDs and low-dose aspirin.[20] Although the number needed to harm is high, the number of patients using the combination of NSAIDs and low-dose aspirin is extensive, subsequently resulting in a large number of gastrointestinal events.[13,32]

Following the report by Lanza et al.,[16] infection with *H. pylori* was regarded as an additive risk factor for gastrointestinal events in NSAID users. Secondary prevention, by testing and subsequently treating *H. pylori* infection in patients with a known history of (complicated) peptic ulcer disease, has proven to be beneficial in low-dose aspirin users at high risk for gastrointestinal complications, but not in other NSAID users.[13] Eradication of *H. pylori* in high-risk patients before the start of NSAID therapy has shown to reduce the incidence of ulceration;[33] however, eradication therapy of *H. pylori* in long-term NSAID users is inferior to using adequate gastroprotection.[23-25] When both *H. pylori* and NSAID use are present, the relative risk for gastrointestinal complications of NSAID use is greater than that of infection with *H. pylori* alone, suggesting that NSAIDs play a more dominant role.[34] A study regarding cost effectiveness demonstrated that *H. pylori* eradication in patients above the age of 50 years was the most effective cost-saving strategy in preventing gastrointestinal complications in NSAID users.[35] In summary, data regarding the exact role of *H. pylori* in peptic ulcer disease are conflicting and the importance of *H. pylori* in ulcer development in NSAID users is still under debate.

Concomitant use of clopidogrel is a controversial risk factor. Only three included guidelines mentioned an increased gastrointestinal risk.[13,14,17] Although clopidogrel was only approved in 1998, its gastrointestinal adverse effects are well known.[29,36] Combinations of different antithrombotics act in a synergistic manner, suggesting that the combination of a traditional NSAID with clopidogrel will also lead to an increased risk of gastrointestinal complications.[37] Recently, studies regarding the interaction between clopidogrel and PPIs were published.[38,39] Concomitant PPI use seems to abolish the cardiovascular protective effects of clopidogrel. With this knowledge, the European Medicines Agency made a public statement about this interaction in May 2009 and discourages concomitant use of a PPI and clopidogrel-containing medicines unless absolutely necessary. This further complicates the preventive strategies as PPIs are the primary choice for gastroprotection in this population.[13,40]

Concomitant use of SSRIs is also a controversial risk factor. A recently published meta-analysis by Loke et al.[41] demonstrated that the odds ratio for upper gastrointestinal hemorrhage in patients using SSRIs alone was 2.36 (95% CI 1.44, 3.85) compared with 6.33 (95% CI 3.40, 11.8) in patients using NSAIDs and concomitant SSRIs. The increased risk of concomitant SSRI therapy on gastrointestinal events in patients using NSAIDs should be taken into account by any physician as both drugs are often prescribed together. At present, SSRIs as a risk factor might be controversial as it has only been recently identified and will need further exploration.

Individual NSAIDs have different gastrointestinal toxicity profiles and, therefore, do not lead to comparable amounts of gastrointestinal complications. Ibuprofen is a traditional NSAID with the lowest gastrointestinal risk, whereas piroxicam has an almost 4-fold higher risk of gastrointestinal complications compared with ibuprofen.[42] Also, the dosage of NSAIDs is of importance in gastrointestinal complications. For example, it is possible that the low risk associated with ibuprofen found in the majority of studies where it is included may be because a low dose is usually used. A study by Gutthann et al.[43] indicated that the risk of upper gastrointestinal bleeding and perforation for ibuprofen at a daily dose of 1500 mg or less was 1.2 compared with 5.8 at daily doses above 1500 mg.

The definition of high dose was not stated in the included guidelines and consensus agreements.

Co-morbidity was recognized as a risk factor. Depending on specialization, authors found severe rheumatoid arthritis, a history of any cardiovascular event, heart failure and diabetes mellitus to be risk factors;[14,16-18] however, patients experiencing any of the mentioned diseases may use more, and higher, doses of medication. Association of co-morbidity with an increased risk of a gastrointestinal event in patients using NSAIDs could therefore well be secondary to concomitant multiple drug use. Cardiovascular risks of NSAID use, with emphasis on selective COX-2 inhibitors, are widespread.

OTC availability contributes to the growing consumption of NSAIDs.[13,22,44,45] Guidelines and consensus agreements on the role of OTC NSAIDs were therefore reviewed in order to examine risk factors in this specific but large group of NSAID users. We hypothesize that gastrointestinal risk in patients using OTC NSAIDs may well be similar to patients using prescribed NSAIDs. Both lower dosing and less frequent use could contribute to a lower gastrointestinal risk than that of prescribed NSAIDs. On the contrary, gastrointestinal risk could be higher because of multiple NSAID use if a NSAID is prescribed by a physician in addition to OTC use or patients might not adhere to recommended dosages or cautions. However, although the risk is difficult to assess, it may not be discarded because of the large numbers of NSAIDs used.[13,24,44,45] OTC NSAID use is difficult to control by physicians; therefore, perhaps guidelines with direct focus on OTC use should primarily be aimed at pharmacists in order to identify patients at risk. This may explain why reviewed guidelines did not address OTC use.

We advise physicians to carefully interrogate for possible OTC NSAID use if a patient is at increased risk for gastrointestinal complications. Moreover, if physicians recommend (OTC) NSAID use, they should always consider gastrointestinal risk factors and take these into account prior to their recommendation. Other options include switching to paracetamol (acetaminophen) or co-prescription of a gastroprotective agent. No studies are currently available that have examined gastrointestinal risks in naive OTC NSAID users. To elucidate this issue, a large clinical trial could be performed where OTC NSAID users with definite gastrointestinal risk factors would randomly be assigned to either of the following options: (i) switching to (OTC) paracetamol; (ii) co-prescription of a PPI; and (iii) no intervention. However, this is not feasible because of ethical concerns with an increased mortality due to gastrointestinal complications in older patients.[46] Without the results of a prospective study, recommendations regarding OTC NSAID use in patients at risk for gastrointestinal complications are not evidence-based.

In this systematic review, we only included guidelines and consensus agreements published in English, which could possibly account for selection bias as the reviewed guidelines are all derived from Western countries, which are accountable for the vast majority of NSAID use; therefore, guidelines and consensus agreements mostly originate from these countries. Another limitation of this study might be our interpretation of the authors' interpretation of analysed guidelines and consensus agreements. A systematic review is as strong as its individual components; however, interpretation of numerous studies is a limitation of all (systematic) reviews. In contrast, although scientific sources of most guidelines and consensus agreements concur, authors' interpretations lead to different recommendations, as shown in this article. This systematic review puts these interpretations into perspective. We included articles that used differing methodology, such as panel discussions and opinion articles, with the terms 'guideline' or 'consensus' present in the title. Although methodology is not consistent, the management of patients using NSAIDs in many countries worldwide is largely dependent on discussed guidelines and consensus agreements.

4. Conclusions

We reviewed guidelines and consensus agreements on risk factors for gastrointestinal events in patients using NSAIDs and identified a history

of (complicated) peptic ulcer disease, older age (cut-off age ranging from 60 to 76 years), concomitant anticoagulant use, concomitant corticosteroid use and multiple NSAID use, including low-dose aspirin, as undisputed definite gastrointestinal risk factors in NSAID users. Several controversial risk factors, including concomitant clopidogrel and SSRI use, require further research. Finally, we found an absence of recommendations regarding OTC NSAIDs in studied guidelines and consensus agreements. OTC NSAID use should be addressed and considered by physicians in the identification of patients at risk for a gastrointestinal event.

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