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# Prescription of and Adherence to Non-Steroidal Anti-Inflammatory Drugs and Gastroprotective Agents in At-Risk Gastrointestinal Patients

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- OBJECTIVES:** Patients with gastrointestinal (GI) risk factors who take non-steroidal anti-inflammatory drugs (NSAIDs) should also take gastroprotective agents (GPAs). No studies have evaluated adherence and reasons for non-adherence to GPA and NSAID therapies.
- METHODS:** This was a prospective, multicenter, observational, longitudinal study. Patients attending rheumatology/orthopedic clinics who were co-prescribed NSAID plus GPA for at least 15 days and had risk factors for GI complications were followed up by telephone call. Optimal adherence was defined as taking the drug for  $\geq 80\%$  of prescribed days. Multivariate logistic regression analysis was used to determine factors associated with non-adherence.
- RESULTS:** Of 1,232 patients interviewed, 192 were excluded because of inaccurate data. Of the remaining 1,040 patients, 74% were prescribed low-dose NSAIDs and 99.8% were prescribed a standard or high-dose GPA. In all, 70% of NSAIDs and 63.1% of GPA prescriptions were short term (<30 days). The majority of patients who were prescribed either an NSAID (92.5%) or GPA (85.9%) started therapy. Optimal adherence to GPA or NSAIDs was reported by 79.7% (95% confidence interval (CI): 76.9–82.2%) and 84.1% (95% CI: 81.7–86.3%) of patients, respectively. More adverse events occurred among patients who reported non-optimal adherence than among patients with optimal adherence to GPA (22.1 vs. 1.9%,  $P < 0.0001$ ). As reasons for non-adherence, patients most frequently cited infrequent/low-intensity rheumatic pain (NSAIDs) or forgetfulness (GPAs). Adverse events and short-term treatment were independent factors associated with poor adherence for both NSAIDs and GPAs. History of uncomplicated peptic ulcer and frequent dosing were additional factors associated with non-adherence to NSAIDs.
- CONCLUSIONS:** Most frequent reasons for non-adherence are infrequent/low-intensity rheumatic pain (NSAIDs) or forgetfulness (GPAs). Short-term treatment and adverse events were associated with poor adherence for both therapies.

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## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for the treatment of pain and inflammation in patients with various musculoskeletal conditions. It is well known that NSAIDs induce gastrointestinal (GI) adverse effects, including serious complications such as upper GI bleeding, perforation, obstruction, and death (1,2). Patients with risk factors are more likely to develop serious complications. Risk factors for GI complications are well known and depend on patient characteristics, medical history, and the type of NSAID prescribed (1,2).

To reduce the risk of these adverse events, different scientific societies and regulatory authorities have developed guidelines and recommendations to indicate that patients with risk factors should receive preventive treatment including, among others, the co-prescription of gastroprotective agents (GPAs), namely a standard dose of proton pump inhibitors (PPIs), misoprostol, or high-dose famotidine (3,4).

Two major challenges to reduce serious GI complications in at-risk patients are the low prescription rates of preventive therapy and poor patient adherence to prescribed GPAs. Several

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studies have reported a lack of correspondence between patterns of NSAID and GPA prescription (5–8), as well as reduced levels of patient adherence to prescribed GPAs, with reported rates of non-adherence ranging from 9 to 71% (9–11). Adherence to GPAs below the optimum level (which is defined as taking GPAs for  $\geq 80\%$  of the prescribed days) has been associated with a 2.5- to 4-fold increase in the risk of upper GI bleeding in patients receiving NSAIDs (9–11).

Although these studies have consistently demonstrated reduced levels of adherence to GPA therapy among NSAID users, several issues remain unresolved. One such issue is that these studies have basically evaluated the adherence to PPI therapy of NSAID users with varying GI risk levels; however, the actual pattern of NSAID prescription in this population and whether patients exhibit differences in adherence to either NSAIDs or GPAs is unclear. Another important concern is the reasons for low adherence. Many patients take multiple drugs, which may be a factor in cases of poor adherence (12), and patients may elect to take these drugs only if they have symptoms. For example, patients may take NSAIDs if they have musculoskeletal pain or a PPI if they have dyspepsia, although the occurrence of these respective symptoms may not be simultaneous. It must be noted that up to 60% of patients developing upper GI complications have no previous abdominal symptoms (13). Based on these considerations, the primary objectives of this study were to determine the levels of adherence to prescribed GPAs and NSAIDs in at-risk patients. Secondary objectives were to describe the type of prescription, and to investigate factors associated with adherence.

## METHODS

### Settings

This was a multicenter, observational, longitudinal study with prospective data collection. The study was conducted between 15 May 2008 and 16 January 2009. There were a total of 296 doctors involved in recruiting patients in 158 different outpatient clinics (mostly rheumatology, traumatology/orthopedic or internal medicine) distributed throughout Spain.

### Patients

Inclusion criteria were (i) patients attending outpatient clinics with a musculoskeletal condition and an indication for NSAID prescription; (ii) age  $\geq 18$  years; (iii) presence of at least one GI risk factor of those described below, and (iv) receipt of prescriptions for both an NSAID and a GPA for a minimum of 15 days. The only exclusion criterion was treatment with a GPA for reasons other than the prevention of NSAID-related complications (e.g., gastroesophageal reflux disease). All included patients signed an informed consent form agreeing to participate in the study.

GI risk factors (3–8) for this study were (i) age  $\geq 60$  years; (ii) a history of peptic ulcer, ulcer complications, or dyspepsia (a marker for increased risk of peptic ulcer, especially in populations with high *H. pylori* infection rates (14–17)); (iii) the use of aspirin, corticosteroids, or anticoagulants in addition to a prescribed NSAID; (iv) the use of a high-dose NSAID or the use of two

NSAIDs. High-dose NSAID, which has been previously defined elsewhere (18,19), included treatment with any NSAID at the maximum dose recommended for the symptomatic treatment of arthritis pain (e.g., diclofenac  $\geq 150$  mg/day, aceclofenac  $\geq 100$  mg/day, meloxicam  $\geq 15$  mg/day, naproxen  $\geq 1,000$  mg/day, piroxicam  $\geq 20$  mg/day, and ibuprofen  $> 1,800$  mg/day). The doses of PPI for gastroprotection were as follows: omeprazole 20 mg/day, lansoprazole 30 mg/day, pantoprazole 20 mg/day, and esomeprazole 20 mg/day. Among the  $H_2$  receptor antagonists, the doses were 40 mg/12 h for famotidine. The appropriate doses for misoprostol were 200  $\mu$ g/6–8 h.

### Questionnaires and follow-up

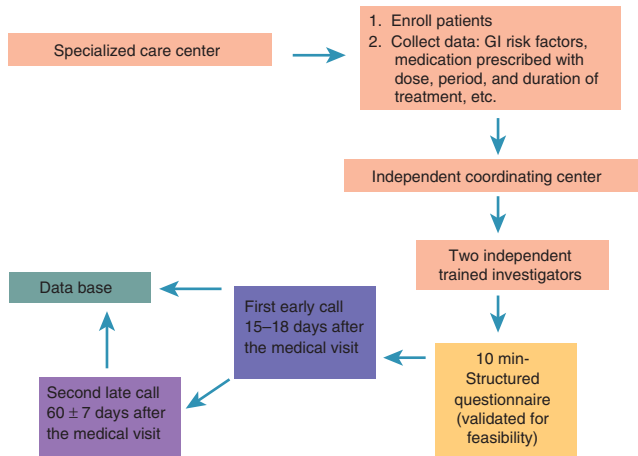
Investigators enrolled consecutive patients (with the above-mentioned inclusion criteria and no exclusion criteria) who agreed to participate in the study for at least 1 month. Investigators collected data in a closed and pre-printed questionnaire that included data concerning demographics (age and sex), GI risk factors, and current medication for pre-existing conditions, as well as doses, duration of use, time of use, and reason for prescription of NSAID plus GPA. Each questionnaire was anonymized, and patients were only identified by a number. Each questionnaire contained a telephone number provided by the patient where they could be reached for follow-up. Once completed, each questionnaire was faxed to the coordinating center and the principal investigator (AL) evaluated the consistency and completeness of the data provided and requested additional information or clarification, if needed.

To be contacted for follow-up, patients signed an informed consent form. They were also informed that they would receive one or two telephone calls from independent researchers who would ask questions concerning their disease and the medication they take within an investigational project.

Patients were followed up with telephone calls at a maximum of two different times. The first contact was an early call within 15–18 days after the medical visit. If the prescription of the NSAID plus GPA was for 30–60 days or longer, then the patients received a second call within a window of  $60 \pm 7$  days. Two independent and trained investigators (MPT and PR) carried out the calls and completed a structured questionnaire that was originally validated in a small group of patients to assess the feasibility of the questions. The questions focused on adherence to NSAID plus GPA therapy and evaluated levels of adherence and reasons for not taking the pills. In general, the call lasted  $\sim 10$  min and patients were asked to provide the number of prescriptions obtained and the number of pills that remained in the package or to be refilled at the end of the interview. The study flow is summarized in **Figure 1**.

### Statistical analysis

Descriptive analysis of the patients included demographic and clinical characteristics, pharmacological treatments, and frequencies of the main variables of the study (rates of adherence, factors associated with adherence and type of prescription). Quantitative variables were analyzed using measurements of central tendency



**Figure 1.** Study flow. Investigators collected consecutive patients who met inclusion and exclusion criteria and who agreed to participate in the study. After data collection, the anonymized information was sent to the coordinating center. Patients were followed up with telephone calls at two different times and the follow-up information was added to the database. GI, gastrointestinal.

(mean and median) and dispersion (95% confidence intervals (CIs), standard deviation, quartiles, and ranges). Qualitative variables were defined according to their absolute and relative frequencies. Student's *t*-test was used to analyze quantitative variables. Categorical variables were analyzed using the  $\chi^2$  test or the Fisher's exact test. Tests were two-tailed with a significance level of 5%. Multivariate analyses were used to determine risk factors of poor adherence to either NSAID or GPA therapy. Optimal adherence was defined as taking GPAs for  $\geq 80\%$  of the prescribed days. Models of logistic regression were constructed based on variables of interest (age, gender, ulcer history, concomitant medications (including aspirin, corticosteroids, and anticoagulants) history of dyspepsia, dose of NSAIDs, use of two NSAIDs, duration of treatment, dose timing, number of pills and reasons for not taking medication) to provide adjusted odds ratios for each factor. A backward selection method was used and those variables with a significance level of  $> 0.2$  were excluded from the model.

Data were analyzed with SAS 8.2 statistical software (SAS Institute, Cary, NC). A sample size of 1,200 patients would provide an error  $< 3\%$  for 50% levels of adherence.

An initial analysis of the data on GPA adherence showed an unexplainably high proportion of patients who did not provide a reason for not starting PPI therapy. This led us to do a manual *post hoc* review of the original data collected during the telephone call. We found that this proportion was lower, since many of those patients had already taken the medication (which was prescribed for 2 weeks) at the time of the call, and were incorrectly introduced into the database as patients who were not taking the medication rather than patients who had finished the prescribed treatment. This made us revise the whole database and the questionnaire to reconfirm that it was the only problem with data entry and the interpretation of questions.

**Table 1.** Demographics of patients and gastrointestinal risk factors

Variable	Mean (s.d.)	95% CI
Age (years)	57.1 + 16.0	56.1, 58.1
Gender	Female: 722 (69.4%)	66.5%, 72.2%
	Male: 318 (30.6%)	27.8%, 33.5%
<i>Main risk factors</i>	N (%) 1,040 (100%)	95% CI
Age $\geq 60$ years	522 (50.2%)	47.1%, 53.3%
History of complicated peptic ulcer	34 (3.3%)	2.3%, 4.5%
History of uncomplicated peptic ulcer	101 (9.7%)	8.0%, 11.7%
History of dyspepsia	304 (29.2%)	26.5%, 32.1%
Co-therapy with anticoagulants	47 (4.5%)	3.3%, 6.0%
Co-therapy with aspirin	82 (7.9%)	6.3%, 9.7%
Co-therapy with non-aspirin antiplatelet agents	32 (3.1%)	2.1%, 4.3%
Treatment with two NSAIDs	77 (7.4%)	5.9%, 9.2%
High NSAID dose	12 (1.2%)	0.6%, 2.1%
Other	68 (6.5%)	5.1%, 8.2%

CI, confidence interval; GI, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs.

The guidelines of the American College of Gastroenterology consider age to be a risk factor when patients are  $> 65$  years of age. The corresponding figure is 366/1,040 (35.2%). Also, the proportion of patients with very high GI risk (patients with a history of complicated ulcer or  $> 2$  risk factors) = 81/1,040 (7.8%). The total number of patients with one or more GI risk factors considering the age cutoff at 65 is 77.3%.

### Ethical considerations

This study complied with all ethical considerations involving human subjects, as adopted by the 18th World Medical Assembly, Helsinki, Finland. All recorded information was obtained following the standard clinical guidelines, and patients were not subjected to any therapeutic or diagnostic experimentation. The study followed standard security and confidentiality measures, complying fully with Spanish legislation regarding data protection (Ley Orgánica de 15/99). The Regional Ethics Committee for Clinical Research, Hospital San Carlos (Madrid) approved this study. The patients' names remained confidential; identification numbers were used instead.

## RESULTS

### Demographics

A total of 296 specialists participated in the study and 1,232 patients agreed to participate, of whom 192 were excluded due to incomplete data in the original questionnaire completed by the investigator ( $n=9$ ), duration of treatment  $< 15$  days ( $n=34$ ), or telephone interview not carried out within the pre-specified time window ( $n=149$ ). Therefore, 1,040 patients were included in the final analysis. **Table 1** presents patients' clinical characteristics.

### Type of prescription

The most common type of anti-inflammatory drug prescribed was traditional NSAIDs (862/1,040, 82.9%); COX-2 selective inhibitors represented 13.1% (136) of all prescriptions. Among traditional NSAIDs, in 682 (79.1%) cases the prescription was below the recommended doses. The standard dose was prescribed in 157 (18.2%) cases. In 568 (65.9%) cases, duration of treatment was short term (<30 days). Among prescriptions for COX-2 selective inhibitors, 31.6% were below recommended doses, 66.2% were for the standard dose, and 61.0% were short-term prescriptions. The majority of prescriptions for traditional NSAIDs (81.7%) were either b.i.d. or t.i.d.; by contrast, 89.7% of COX-2 selective inhibitor prescriptions were to be taken once daily.

Among patients who were prescribed a GPA, 1,028 (99.4%) were also prescribed a PPI, while the remaining patients were prescribed H<sub>2</sub> receptor antagonists (0.39%) or misoprostol (0.19%). The doses of PPI prescribed were the approved dose for the indication of GI prevention of NSAID damage in 70.6% of cases, while 28% of patients were prescribed higher doses. PPI prescription was once daily in 95.6% of cases. Prescribed PPI treatment was short term (<30 days) in 63.1% of cases; 512 (49.2%) patients were additionally taking other types of medication (different from NSAIDs or GPAs) for different reasons.

### Adherence to treatment

The telephone interview was conducted with the patient in 92.4% of cases. In the remaining 7.6% of cases, a family member of the patient was also involved in the interview.

### NSAIDs

In 92.5% (962/1,040) of cases, the patient reported starting NSAID treatment. Among 77 patients (1 case with data missing) who did not start the prescribed NSAID, the main reasons for not initiating treatment were quite diverse: not properly understanding the doctor's instructions was the most frequently cited reason (24 [35.8%]), followed by infrequent/low-intensity pain (16 [23.9%]), fear of adverse events (11 [16.4%]) and taking medications other than those prescribed for pain (13 [19.4%]).

Of the patients who did initiate therapy, 233 (24.2%) failed to take the prescribed NSAID at some point for a mean of 12.2±19.1 days. **Table 2** summarizes the reasons given by patients for not taking the prescribed NSAID at some point during treatment which were infrequent/low-intensity pain (29.4%), development of adverse events (15.7%), that the prescribed NSAID was ineffective (9.3%), forgetfulness (12.5%), and not getting a second prescription (31.4%).

The majority of patients (79.7%; 95% CI: 76.9–82.2%) exhibited optimal adherence, taking the prescribed NSAID for 80% or more of the days prescribed.

### GPAs

In 85.9% (893/1,040) of cases, the patient reported starting GPA therapy. Reasons for not initiating GPA treatment (146 patients, 1 case with data missing) were infrequent/low-intensity pain

**Table 2.** Main reasons reported by patients for not taking the prescribed NSAID or GPA at some point (any day) during treatment among those who started therapy

Reason for lack of compliance	Number (%)	95% CI
<b>NSAIDs</b> N=233 (100%)		
Adverse event	32 (15.7%)	11.0%, 21.4%
Not having enough rheumatic symptoms	60 (29.4%)	23.2%, 36.2%
Taking a different drug, or the prescribed drug was not effective	19 (9.3%)	5.7%, 14.1%
Forgetfulness	26 (12.2%)	8.5%, 18.1%
Not getting a second prescription	64 (31.4%)	25.1%, 38.2%
Other	3 (1.4%)	0.3%, 4.2%
Missing	29	—
<b>GPAs</b> N=48 (100%)		
Adverse event	3 (7.9%)	1.7%, 21.4%
Infrequent/mild-intensity pain	15 (39.5%)	24.0%, 56.6%
Taking a different drug, or the prescribed drug was not effective	1 (2.6%)	0.1%, 13.8%
Forgetfulness	18 (47.4%)	31.0%, 64.2%
Other	1 (2.1%)	0.1%, 13.8%
Missing	10	—

CI, confidence interval; GPA, gastroprotective agent; NSAIDs, non-steroidal anti-inflammatory drugs.

(64 [43.8%]), fear of adverse events (24 [16.4%]), taking different analgesics (19 [13.0%]), not understanding the doctor's instructions (15 [10.3%]), and taking too many/unnecessary pills (5 [3.4%]). Fifteen (10.3%) did not provide an answer, and three patients (2.1%) gave other reasons.

Of the patients who initiated GPA therapy, 48 (5.4%) failed to take the drug at some point for a mean of 8.5±25.9 days. **Table 2** summarizes the reasons given by patients for not taking the prescribed GPA at some point during treatment which were forgetfulness (47.4%) and the absence of either rheumatic or abdominal symptoms (39.5%). Overall, 84.1% took the drug for 80% or more of the days prescribed.

Of patients who reported initiating NSAID therapy, 9.3% did not take concomitant GPA therapy at any point. In 11% of cases (95% CI: 9.0–13.2%), GPA therapy either was not initiated, or was taken <80% of the time. Only eight patients had short-term prescription of GPA (<30 days) together with longer (>30 days) prescription of NSAIDs.

To assess the concordance between patients' reported behavior and actual behavior, participants were asked to count the pills remaining from the last prescription at the end of the interview. Concerning GPA prescriptions, in 338/1,040 (32.5%) cases the pill count was not performed because the patient had not started therapy, or was unable to perform the count for other reasons.

**Table 3. Factors associated with poor adherence to NSAID treatment**

Variable <sup>a</sup>		N (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI) <sup>a</sup>
History of uncomplicated peptic ulcer	No	160 (85.1%)		
	Yes	28 (14.9%)	1.8 (1.1, 2.9)	2.3 (1.4, 3.9)
Non-aspirin antiplatelet treatment	Yes	1 (0.5%)		
	No	187 (99.5%)	6.8 (0.9, 50.7)	—
Antiplatelet treatment	Yes	14 (7.5%)		
	No	174 (92.5%)	1.6 (0.9, 2.8)	—
Number of pills/day	Once daily	39 (20.7%)		
	More than once daily	149 (79.3%)	1.6 (1.1, 2.3)	1.6 (1.1, 2.5)
Length of prescription	>4 weeks	32 (17.8%)		
	≤4 weeks	148 (82.2%)	2.4 (1.6, 3.6)	2.7 (1.7, 4.2)
Adverse events	No	156 (83.0%)		
	Yes	32 (17.0%)	12.4 (6.2, 24.6)	14.9 (7.1, 31.2)

CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio.  
<sup>a</sup>Adjusted ORs in the final model.  
 ORs of variables that were not statistically significant in the logistic regression model are not reported.

Among patients who counted the pills, there was agreement in 94.7% of cases between the patients' self-report and the actual count. Regarding NSAID prescriptions, 55% of patients did not perform the pill count; among those who did, agreement was present in 91% of cases. For both drug types, the highest disagreement occurred in patients who reported adherence between 20 and 80% (GPAs: 27/38, 71%; NSAIDs: 8/30, 26.7%).

### Adverse events

The frequency of adverse events was higher in patients who reported not optimal adherence to either GPA or NSAID prescriptions; 22.1% (35/158) of patients with low adherence (<80%) to GPA had an adverse event, compared with 1.9% (16/838) of patients who were optimally adherent ( $P<0.0001$ ). Similarly, 17.0% (32/188) of patients who were not optimally adherent to NSAIDs had an adverse event, compared with 1.6% (12/737) of optimally adherent patients ( $P<0.0001$ ). Adverse events were GI (30 dyspepsia, 3 diarrhea, and 1 bleeding event) in most cases (34/49). The remaining events were non-GI, including cardiovascular/renal (hypertension, edema ( $n=4$ ), allergic reactions ( $n=2$ ), headache ( $n=1$ ), and unspecified ( $n=13$ )).

### Multivariate analysis for adherence

Univariate analysis revealed that of all clinical variables considered, concomitant use of a non-aspirin antiplatelet drug, overall use of any antiplatelet drug, high-dose GPA (PPI), short-term GPA treatment, and the presence of adverse events were associated with poor patient adherence to GPA prescription, while history of uncomplicated peptic ulcer disease, use of a non-aspirin antiplatelet drug, dosing regimen for NSAID treatment,

short-term NSAID treatment, and the presence of adverse events were associated with poor patient adherence to NSAID prescription. Logistic regression analysis demonstrated that of all variables considered in the models, short-term prescription of GPA therapy and the presence of adverse events were independent determinants for poor adherence to the prescribed GPA. The presence of uncomplicated ulcer history, short-term NSAID prescription, frequent NSAID dosing, and the presence of adverse events were associated with poor adherence to the prescribed NSAID (Tables 3 and 4). The major determinants of poor adherence to either NSAID or GPA prescription were the development of adverse events, which in most of cases were GI adverse events (dyspepsia being the most common).

We conducted additional analysis with (i) age as a risk factor when >65 years, instead of 60 years; (ii) the presence of very high GI risk, as defined by the guidelines of the American College of Gastroenterology (3), and (iii) excluding history of dyspepsia as a risk factor. Neither the presence/absence of very high GI risk, nor the presence/absence of dyspepsia showed statistically significant differences in either NSAID or GPA adherence; however, patients with very high GI risk showed a trend for greater adherence to GPAs and less adherence to NSAIDs. When compared with patients <65 years old, those >65 years of age were associated with a trend ( $P=0.07$ ) toward higher levels of adherence to GPA, but not NSAID therapy (similarly to the results obtained by using 60 years of age as the cutoff point). When this variable ( $\geq 65$  vs. <65 years of age) was included in the logistic regression model, it was not independently associated with poor adherence to GPA (data not shown). In addition to short-term prescription of GPA therapy and the presence of adverse events, being <65 years was

**Table 4. Factors associated with poor adherence to GPA treatment**

Variable <sup>a</sup>	Crude %	N (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI) <sup>a</sup>
Age (years)	≥60	72 (45.6%)		—
	<60	86 (54.4%)	1.3 (0.9, 1.8)	
History of complicated peptic ulcer	Yes	2 (1.3%)		—
	No	156 (98.7%)		
Non-aspirin antiplatelet treatment	Yes	1 (0.6%)	2.9 (0.7, 12.2)	—
	No	157 (99.4%)		
Antiplatelet treatment	Yes	9 (5.7%)	5.8 (0.8, 43.0)	—
	No	149 (94.3%)		
Dose of gastroprotectant	Low	2 (1.3%)	2.1 (1.1, 4.3)	—
	Standard	93 (59.6%)	0.9 (0.2, 4.5)	
	High	61 (39.1%)	1.9 (0.4, 8.5)	
Length of prescription	>4 weeks	34 (21.8%)		
	≤4 weeks	122 (78.2%)	2.3 (1.5, 3.5)	2.4 (1.6, 3.7)
Adverse events	No	123 (77.9%)		
	Yes	35 (22.1%)	14.6 (7.9, 27.2)	15.5 (8.2, 29.3)

CI, confidence interval; GPA, gastroprotective agent; OR, odds ratio.  
<sup>a</sup>Adjusted ORs in the final model.  
ORs of variables that were not statistically significant in the logistic regression model are not reported.

independently associated with poor GPA adherence (odds ratio: 2.2; 95% CI: 1.3–3.9) if the analysis was restricted to patients who reported initiating the prescribed NSAID therapy.

## DISCUSSION

This study focuses on patients' adherence to both NSAIDs and GPAs. Previous studies showed low rates of GPA prescription to at-risk patients receiving NSAIDs, and low levels of adherence to GPA prescriptions among those who did receive co-therapy (9), which was in turn associated with the increased risk of GI complications (10,11). However, these studies did not investigate the reasons for poor adherence or the determinants of poor adherence with regard to GPAs or NSAIDs. We believe that these aspects are of paramount importance because they are probably linked. Here, we have investigated these features by examining adherence to both GPA and NSAID therapies using a different approach, which is based on the direct questioning of patients concerning their reasons for not taking the prescribed medication. Consequently, we were able to discriminate and report on two aspects of the same spectrum: (i) failure to initiate the prescribed treatment and (ii) lack of adherence to the prescribed drugs.

Rates of adherence to both therapies were high; however, contrary to what may be expected the proportion of patients who did not initiate the prescribed GPA therapy was higher than the proportion that did not initiate NSAID therapy. This pattern

may be due to the fact that patients who start NSAID therapy because they seek rheumatic pain relief do not necessarily experience GI symptoms, and some patients may not be aware of the increased GI risk associated with NSAID use. Interestingly, among patients who did not initiate NSAID therapy, failure to properly understand their doctor's instructions was most often cited as the primary reason, suggesting that this aspect should be taken into consideration during the prescription process. On the contrary, among those who did not initiate GPA therapy, most patients did not do so because they had no (or mild) GI symptoms. Among patients who actually started therapy, a high proportion reported optimal drug adherence (defined as taking the prescribed drug >80% of the days prescribed) for both NSAIDs and GPAs; this proportion was actually higher than reported in other studies (9–11), but is in agreement with the increasing trend of concomitantly prescribing a GPA to NSAID users (20). Our different methodological approach may explain the findings of higher adherence rates.

Patients may falsely report high compliance levels because they have a false perception of compliance. We have tried to evaluate this possibility by asking patients to report on the number of NSAID and GPA pills remaining at the time of the follow-up interview. We could not obtain that information from all patients; however, among those who could actually count the pills, we found a high degree of agreement between the reported adherence and the number of pills taken from the prescribed boxes for both GPAs and NSAIDs.

Among patients reporting poor adherence to medication, there was a higher level of adherence to GPA than to NSAID therapy; the reasons for poor adherence were different for the two drug types. Although the main reasons given for stopping NSAID therapy were infrequent/low-intensity rheumatic pain or developing adverse events, the main reason for stopping GPA therapy was forgetfulness, followed by the absence of either rheumatic or abdominal symptoms. If we consider that some of the reasons given (e.g., not getting a second prescription) may also reflect infrequent/low-intensity rheumatic pain, then this was the most often-cited reason for non-adherence to prescribed NSAIDs. These findings reveal the primary underlying reasons driving drug use behavior in clinical practice, demonstrating that a substantial number of patients with chronic musculoskeletal conditions take their NSAID prescription irregularly depending on the level of pain. These results also document that the development of adverse events (especially GI-related adverse events) is another major factor affecting drug use. On the contrary, the main reason for not taking the GPA is probably linked to lack of GI symptoms in most cases.

The development of adverse events is a well-known characteristic of NSAID therapy. The design and size of this study did not allow us to detect GI complications or determine whether poor adherence was associated with this serious adverse event. However, we were able to evaluate other patient-reported minor adverse events, which often are not recorded in databases, but are suspected to be the main reasons for stopping NSAID use (2). It should be noted that dyspepsia was the most commonly reported adverse event, and that patients who were non-adherent to GPA therapy had a significantly higher risk of this type of adverse event.

This study also investigated clinical determinants of poor adherence to either NSAID or GPA prescriptions. History of peptic ulcer disease and the presence of adverse events were predictors of poor adherence to NSAID prescriptions and seem related to the well-known GI risk associated with NSAIDs. Concomitant use of a non-aspirin antiplatelet agent was also associated with poor adherence to GPA prescriptions, and may be related to the current warning from regulatory agencies to take PPIs together with clopidogrel (21), although eventually this did not emerge as an independent factor. Frequent dosing (more than once daily) was a predictor of poor adherence to NSAID but not GPA prescriptions, which may be due to the fact that PPIs are taken once daily, while NSAIDs are taken several times per day. Short-term treatment (<30 days) was a predictor of poor adherence for both therapies. The reason for this is unclear, because short-term NSAID treatment was the most frequent prescription type in our study. It is possible that patients who received longer periods of therapy suffered from more severe musculoskeletal diseases and pain, which would increase adherence during the relatively short period of observation (15 and 60 days); however, this characteristic was not recorded in our study.

This study has also evaluated the prescription characteristics of both NSAIDs and GPAs in patients who are at risk for GI complications. NSAID prescriptions were usually short-term and at

lower than-recommended doses, in clear contrast with the type of treatment and dosing prescribed for similar indications in randomized controlled trials (22,23). However, the doses of GPA prescribed were either standard or high. This prescription pattern may be guided by the perceived GI risk with NSAID treatment in an attempt to minimize adverse events, given that dose and duration are two factors linked to increased risk of upper GI complications (2).

Our study has several strengths and limitations. This study evaluated a real clinical sample, and direct contact with patients allowed us to take a different approach to evaluate the patient-reported reasons for non-adherence, a factor that studies based on the data extracted from database platforms cannot report. This study is limited by the lack of a direct, objective measure of prescription use. Instead, we had to rely on the patients' self-reporting, which may introduce recall bias. We have tried to limit the impact of recall bias by having patients report the number of pills remaining in their prescriptions. Among patients who were able to provide this information, we found a high level of agreement, which supports the validity of our study. In any case, it must also be recognized that having issued a prescription does not mean that patients will take the medication, an aspect that cannot be controlled in database studies. Another limitation is that our study reports mostly on short-term NSAID and GPA therapy, which we found to be the most frequent type of prescription in clinical practice. We did not evaluate the long-term use of these drugs, which might have provided different results. The fact that most patients received short-term prescriptions justified the early telephone call to interview patients about adherence, because a later call might have had a negative impact on the accuracy of our data. It is possible that the study design induced a selection bias for patients who were prescribed short-term and not long-term treatment.

In summary, this study investigated the type of prescription, rate of adherence, and reasons for non-adherence to NSAID and GPA therapy in patients at increased risk of developing GI-related adverse events. NSAIDs and GPAs were prescribed short term in most cases. More subjects initiated NSAID than GPA therapy. We report high levels of adherence to both NSAID and GPA therapies, which supports recent data suggesting an important time trend decrease in the rate of upper GI complications in our country (24). Still, there were more side effects among patients with non-optimal adherence to GPA. Not understanding the doctor's instructions regarding drug use, infrequent/mild-intensity pain, and forgetfulness were the most frequently cited reasons for non-adherence. Adverse events and short-term treatment were the main clinical predictors of poor adherence for both NSAIDs and GPAs. History of peptic ulcer and frequent dosing were additional factors for poor NSAID adherence. We believe that these findings are relevant to attempts to improve adherence to both GPA and NSAID prescriptions among at-risk patients.

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**CONFLICT OF INTEREST**

**Guarantor of the article:** Angel Lanas, MD, DSc.

**Specific author contributions:** Designed the study: Angel Lanas and Javier Zapardiel; drafted the first version of the manuscript: Angel Lanas; made the phone calls: Mónica Polo-Tomás and Pilar Roncalés; conducted the statistical analysis: Miguel Angel Gonzalez; all authors interpreted the results and contributed to the subsequent drafting and versions of the manuscript.

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**Potential competing interests:** Angel Lanas is an advisor to AstraZeneca, Pfizer, and Nicox. Miguel A. Gonzalez works for Quintiles, an external company engaged in statistical support for companies including AstraZeneca. Javier Zapardiel was an employee of AstraZeneca.

**Study Highlights****WHAT IS CURRENT KNOWLEDGE**

- ✓ Patients with gastrointestinal (GI) risk factors who require non-steroidal anti-inflammatory drugs (NSAIDs) need prevention therapies to reduce the risk of serious GI complications.
- ✓ Several studies have shown that these at-risk patients have low prescription rates of prevention therapy, and that patients have poor adherence to gastroprotectants.
- ✓ Poor adherence to gastroprotective therapy in patients who are prescribed NSAIDs has been associated with and increased risk of upper GI bleeding.

**WHAT IS NEW HERE**

- ✓ Low-dose, short-term non-steroidal anti-inflammatory drug (NSAID) therapy is the most commonly issued prescription pattern for at-risk gastrointestinal (GI) patients in clinical practice in Spain.
- ✓ A substantial number of patients co-prescribed with NSAIDs and a proton pump inhibitor (PPI) do not start gastroprotective therapy; however, 79.7 and 84.1% of patients reported optimal adherence to either NSAID or PPI therapy, respectively.
- ✓ Infrequent/mild pain and forgetfulness were the most frequent reasons cited for non-adherence to NSAIDs or gastroprotectants.
- ✓ Adverse events and short-term treatment were the main predictors of poor adherence for both NSAIDs and gastroprotectants. History of peptic ulcer and frequent dosing were additional factors associated with non-adherence to NSAIDs. There were more adverse events among patients with non-optimal adherence to gastroprotectants than among patients with good adherence.

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