Patient-reported adherence to coprescribed proton pump inhibitor gastroprotection in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis patients using nonsteroidal anti-inflammatory drugs

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Background: Patients with osteoarthritis (OA), rheumatoid arthritis (RA), or ankylosing spondylitis (AS) are commonly treated with nonsteroidal anti-inflammatory drugs (NSAIDs), sometimes with a concomitant gastroprotective proton pump inhibitor (PPI). The present study examines real-life patient adherence to PPIs when coprescribed with NSAIDs.

Methods: This retrospective medical record survey identified patients diagnosed with OA, RA, or AS who had PPIs coprescribed with NSAIDs for prevention of NSAID-associated gastrointestinal ulcers. Actual NSAID and PPI intake was retrospectively recorded using a self-reported questionnaire. Adherence to PPI treatment was assessed using descriptive statistics.

Results: In total, 96 patients (69% female, mean age 67 years, 72% OA, 16% RA, 12% AS) were included. The mean patient-reported adherence to coprescribed PPIs was 73%–81%. The percentage of patients with a self-reported adherence of ≥80% was 26%. No predictive factors for low adherence could be identified.

Conclusion: Despite doctors’ instructions to use PPIs concomitantly with NSAIDs, the mean patient-reported adherence to coprescribed PPIs in this population indicates a risk of a “gastroprotective treatment gap”. The patients’ adherence to gastroprotective PPIs for the prevention of NSAID-associated upper gastrointestinal ulcers can be improved.

Keywords: patient adherence, proton pump inhibitors, nonsteroidal anti-inflammatory drugs, gastroprotection, osteoarthritis, self-reported questionnaires

Introduction

Patient adherence to medication is necessary if clinical treatment regimens are to be successful and associated with positive patient outcomes.1–3 However, poor patient adherence to prescribed treatments is a common issue, seen almost independently of the therapeutic area. In patients with arthritis, adherence ranges from 55% to over 80% depending on the drug studied.4

Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin and selective cyclooxygenase-2 inhibitors, are a widely used treatment in arthritis.5,6 Adverse events, for example, gastrointestinal events like peptic ulcers, are the main concern of NSAID treatment.7–11 These may also lead to disruption of NSAID treatment, potentially reducing both positive clinical outcomes and elevating health care costs.12

There is strong evidence that the risk of ulcers and bleeding in the upper, but not lower, gastrointestinal tract may be decreased by concomitant therapy with proton
pump inhibitors (PPIs).\textsuperscript{13} Concomitant gastroprotective
treatment with a PPI is also recommended in guidelines as a
therapy to lower the risk of NSAID-induced gastrointestinal
side effects.\textsuperscript{14,15} Adherence to PPI therapy is important
in NSAID-treated patients, and the “gastroprotection gap”,
such as low utilization of gastroprotective strategies and low
adherence to gastroprotection among users of NSAIDs at high
risk of adverse gastrointestinal events,\textsuperscript{16,17} increases the risk
of gastrointestinal events, death, and health care costs.\textsuperscript{12,18–20}
Knowledge of real-life patient adherence to PPIs in NSAID-
treated patients is lacking.

This study specifically focused on measuring self-
reported adherence to PPIs over a 7-day period in patients
with osteoarthritis (OA), rheumatoid arthritis (RA), or anky-
losing spondylitis (AS) linked to their intake of coprescribed
NSAID treatment.

Patients and methods
Study design and objectives
This was a retrospective, cross-sectional, observational
study to assess patient-reported adherence to PPI treat-
ment when coprescribed NSAID treatment (Anatomical
Therapeutic Chemical Classification M01A, except M01AH
and M01AX) for the prevention of upper gastrointestinal
side effects associated with NSAID treatment in patients
with OA, RA, or AS in Sweden. Patients should have been
 instructed by their physician to take a PPI on every day of
NSAID intake. The study was approved by the regional
ethical review board of Stockholm (DNR 2011/2118-31/3)
and registered at ClinicalTrials.gov (NCT01519375). The
study was conducted in accordance with the principles stated
in the Declaration of Helsinki.

Patient population
Male and female patients, ≥18 years of age, with a diagnosis
of OA, RA, or AS were consecutively identified from medical
records. The patients were required to have current prescrip-
tions of oral NSAID treatment and PPIs for the prevention
of NSAID-associated gastrointestinal ulcers, with a doctor’s
instruction to use the drugs on the same day. Patients were
excluded if they were participating in any other trial involving
a PPI or an NSAID, had been prescribed a PPI as an acute
treatment for gastrointestinal events or symptoms (eg, gas-
trointestinal ulcer, dyspepsia, gastritis, or gastroesophageal
reflux disease) within the last 8 weeks, if they reported taking
NSAIDs on fewer than three of the reported days, or if they
were unable to complete a study-specific patient self-reported
questionnaire (SRQ). Seven primary care centers and one
rheumatology center participated in the study. Diagnosis
of OA, RA, or AS was according to the clinical practice
each participating center. Data were collected between
March and May 2012.

Study conduct
Patients who fulfilled the inclusion criteria submitted a signed
informed consent form and a completed SRQ to the investi-
gators. Data on PPIs and NSAIDs were recorded in separate
sections of the SRQ. The first question in each section asked
patients about their general use of the drug. Patients were
then asked to retrospectively specify their NSAID and PPI
intake during the previous 7 days using “yes”, “no”, or “do
not recall” for each specific day. The data were entered into
a web-based case report form together with complementary
information from patients’ medical records on disease char-
acteristics and prescribed medications.

Assessing adherence
The level of adherence to PPIs was assessed retrospectively
over a 7-day period using the SRQ. The objective was to
assess patient-reported adherence to PPI treatment on actual
days of NSAID treatment and to assess the proportion of
patients with reported adherence ≤80%. For the primary
variable, adherence to PPI treatment was defined as the
proportion of NSAID treatment days on which the patient
also indicated taking a PPI.

Adherence to the PPI was then calculated as the mean per-
centage of adherence in the total study population, assessed
for all patients using two different methods. The first was a
more conservative approach, where adherence was calculated
using only the answers concerning PPI intake for the days
where a definite “yes” or “no” for adherence was available.
In the second and less conservative (sensitivity) approach, a
day with non-reported PPI intake data or where the answer
for PPI intake was “do not recall” was considered to be a
day of PPI nonadherence, if NSAID intake on the same day
was “yes”.

Statistical analysis
All data were analyzed using descriptive statistics. Factors
predictive of low adherence were tested using logistic regres-
sion. Data are presented using summary statistics.

Results
Patient demographics
In total, 74% (134/180) of the patients who received a ques-
tionnaire completed it. Of these, 96 patients (69% females,
mean age 67 years) fulfilled all inclusion criteria and were included in the final analyses. The majority of the excluded 38 patients only reported taking NSAIDs less than 3 days per week. Seventy-two percent of the patients had a diagnosis of OA, 16% of RA, and 12% of AS; 39% and 22% had medical record histories of dyspepsia and gastroesophageal reflux disease, respectively.

Drugs prescribed
The three NSAIDs most commonly used by patients were diclofenac (34%), naproxen (24%), and ketoprofen (20%, Figure 1). The most common PPI was omeprazole, used by 94% of patients.

Patient-reported adherence
Overall patient-reported adherence to coprescribed PPIs when taking NSAIDs (calculated as a mean percentage of all patients) was 81.1% (Figure 2A) and 73.4% (Figure 2B) using the conservative and less conservative approach, respectively. The holistic interpretation of adherence data from six patients had an effect on the mean overall adherence in the less conservative (sensitivity) approach (Table 1), resulting in a marked and lowered adherence for the total population.

Overall, six patients reported “yes” on one day of PPI intake and then had missing data for the remaining 6 days. All responded “never take PPI” or “I refrain from taking PPI on at least 3 days a week” to the general question on PPI intake over a longer period of time. One patient reported a “no” on one day of PPI intake and then had missing data for the remaining 6 days, but the adherence did not change when analyzed using the less conservative approach.

Twenty-six percent of the patients had a self-reported adherence of <80%, calculated using the conservative approach (Figure 3). Adherence differences between high-dose and low-dose NSAIDs, type of NSAID drug, sex, and diagnosis of OA, RA, or AS were tested, but no significant differences were detected. No factors predictive of low adherence could be identified.

Discussion
Few studies have assessed patient adherence to medication for the chronic treatment of nonmalignant pain. Here a
Table 1 Patient-reported adherence for seven patients, including general questions on PPI intake over a longer period of time and PPI intake on actual days of NSAID treatment over a 7-day period

<table>
<thead>
<tr>
<th>Question 1</th>
<th>Question 2</th>
<th>I took PPIs yesterday</th>
<th>I took PPIs 2 days ago</th>
<th>I took PPIs 3 days ago</th>
<th>I took PPIs 4 days ago</th>
<th>I took PPIs 5 days ago</th>
<th>I took PPIs 6 days ago</th>
<th>I took PPIs 7 days ago</th>
<th>Adherence conservative approach</th>
<th>Adherence less conservative approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;If you think about what you usually do over a period spanning several weeks, do you (for whatever reason) refrain from taking PPIs?&quot;</td>
<td>&quot;If you only consider the last 7 days, when have you been using the PPIs? Please tick ‘yes’, ‘no’ or ‘do not recall’ for each day. Today is the day you received the questionnaire in your hand.&quot;</td>
<td>Missing data</td>
<td>Yes</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>100%</td>
<td>14%</td>
</tr>
<tr>
<td>Response, seven individual patients (P) (P1–P7):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1 I refrain from taking PPIs at least 3 days per week</td>
<td>Missing data</td>
<td>Yes</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>100%</td>
<td>14%</td>
</tr>
<tr>
<td>P2 I refrain from taking PPIs at least 3 days per week</td>
<td>Missing data</td>
<td>Yes</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>100%</td>
<td>14%</td>
</tr>
<tr>
<td>P3 I refrain from taking PPIs at least 3 days per week</td>
<td>Yes</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>100%</td>
<td>14%</td>
</tr>
<tr>
<td>P4 I never take PPIs</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>No</td>
<td>0%</td>
</tr>
<tr>
<td>P5 I refrain from taking PPIs at least 3 days per week</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Yes</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>100%</td>
<td>14%</td>
</tr>
<tr>
<td>P6 I refrain from taking PPIs at least 3 days per week</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Yes</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>100%</td>
<td>25%*</td>
</tr>
<tr>
<td>P7 I refrain from taking PPIs at least 3 days per week</td>
<td>Missing data</td>
<td>Yes</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>Missing data</td>
<td>100%</td>
<td>25%*</td>
</tr>
</tbody>
</table>

Note: *Only 4 days of NSAID intake.

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.
SRQs are easy to use, cheap, measure adherence at source, and provide direct feedback. One disadvantage of the SRQ method is that it only provides an overall estimate of adherence over the specified time period. It may also be subject to “answering bias”, where only a selection of patients actually respond to the SRQ, and the adherence may appear higher than when measured directly in the full study population. Further, adherence rates also tend to increase when patients know that they are being monitored, ie, so-called “pleasing bias”.

The retrospective SRQ method was used in this study because it may provide a more accurate indication of true patient level adherence, since patients’ answers concern actual, real-life drug intake and reduce the bias of patients being reminded to take medication merely by participating in the study.

Patients in this study received the SRQs from and returned them to their treating physician, which may have increased adherence. This pleasing bias may also have made nonadherent patients less willing to participate in the study, thereby also influencing the patient-reported adherence rate that corresponds with rates seen previously.

The potential risk of overestimating patient adherence with this method was analyzed by taking both a conservative and a less conservative (sensitivity) approach to the data in this study. The conservative analysis may have overestimated mean patient adherence because it excluded data where PPI intake on an NSAID day was uncertain. On the other hand, the less conservative approach may have underestimated mean patient adherence. However, the less conservative approach is supported by the patients’ responses regarding long-term PPI intake patterns.

Although patients in this study were asked in the SRQ to state their drug intake for the previous 7 days, they still may have incorrectly recalled the drugs that they took over this short period. Further, the low number of patients in this study makes generalization of the results difficult because even a few patients may have had a large impact on overall adherence rates. Nevertheless, the adherence rates reported here are very similar to previous studies in general and within the same field.

The results indicate that there is a “gastroprotection gap” in approximately 20%–30% of NSAID-treated patients with OA, RA, or AS who are at risk of adverse upper gastrointestinal events. Estimates of the elevated risk of upper gastrointestinal events range from 1.8-fold to 4.0-fold in patients with inadequate gastroprotective agent protection or poor PPI adherence. Moreover, for every 10% decrease in adherence to PPI, the risk of upper gastrointestinal bleeding/ulcers and upper gastrointestinal bleeding alone increases by 9% and 6%, respectively. Similar results were shown in other studies. Since the risk of gastrointestinal events and death in nonadherent patients is increased and also associated

![Figure 3 Distribution of patients with a reported adherence to PPIs ≥80% using the conservative approach.](https://www.dovepress.com/)

**Abbreviation:** PPI, proton pump inhibitor.
with a societal economic burden,12–18 further studies on how to alleviate the problem of poor adherence to coprescribed PPI gastroprotective therapy in this vulnerable population of patients are needed.

Conclusion
In this study, the mean patient-reported adherence to coprescribed PPI in patients with OA, RA, or AS who were instructed to take PPIs on the same day as taking NSAIDs for gastroprotection was estimated to be 73%–81%. The level of patient adherence to PPI therapy in this group corresponds to that seen previously in registry studies, and indicates that there is still room for improvement in patient adherence to PPIs when used for the prevention of NSAID-associated upper gastrointestinal ulcers.

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References


