The risk of bleeding with duloxetine treatment in patients who use nonsteroidal anti-inflammatory drugs (NSAIDs): analysis of placebo-controlled trials and post-marketing adverse event reports

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Purpose: To assess the safety of duloxetine with regards to bleeding-related events in patients who concomitantly did, versus did not, use nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin.

Methods: Safety data from all placebo-controlled trials of duloxetine conducted between December 1993 and December 2010, and post-marketing reports from duloxetine-treated patients in the US Food and Drug Administration Adverse Event Reporting System (FAERS), were searched for bleeding-related treatment-emergent adverse events (TEAEs). The percentage of patients with bleeding-related TEAEs was summarized and compared between treatment groups in all the placebo-controlled studies. Differences between NSAID user and non-user subgroups from clinical trial data were analyzed by a logistic regression model that included therapy, NSAID use, and therapy-by-NSAID subgroup interaction. In addition, to determine if higher duloxetine doses are associated with an increased incidence of bleeding-related TEAEs, and whether the use of concomitant NSAIDs might influence the dose effect if one exists, placebo-controlled clinical trials with duloxetine fixed doses of 60 mg, 120 mg, and placebo were analyzed. Also, the incidence of bleeding-related TEAEs reported for duloxetine alone was compared with the incidence in patients treated with duloxetine and concomitant NSAIDs. Finally, the number of bleeding-related cases reported for duloxetine in the FAERS database was compared with the numbers reported for all other drugs.

Results: Across duloxetine clinical trials, there was a significantly greater incidence of bleeding-related TEAEs in duloxetine- versus placebo-treated patients overall and also in those patients who did not take concomitant NSAIDs, but no significant difference was seen among those patients who did take concomitant NSAIDs. There was no significant difference in the incidence of bleeding-related TEAEs in the subset of patients treated with duloxetine 120 mg once daily versus those treated with 60 mg once daily regardless of concomitant NSAID use. The combination of duloxetine and NSAIDs was associated with a statistically significantly higher incidence of bleeding-related TEAEs compared with duloxetine alone. A similarly higher incidence of bleeding-related TEAEs was seen in patients treated with placebo and concomitant NSAIDs compared with placebo alone. Bleeding-related TEAEs reported in the FAERS database were disproportionately more frequent for duloxetine taken with NSAIDs compared with the full FAERS background, but there was no difference in the reporting of bleeding-related TEAEs when the cases reported for duloxetine taken with NSAIDs were compared against the cases reported for NSAIDs alone.

Conclusion: Concomitant use of NSAIDs was associated with a higher incidence of bleeding-related TEAEs in clinical trials regardless of whether patients were taking duloxetine or placebo; bleeding-related TEAEs did not appear to increase along with duloxetine dose regardless of
NSAID use. In spontaneously reported post-marketing data, the combination of duloxetine and NSAID use was not associated with an increased reporting of bleeding-related events when compared to NSAID use alone.

Keywords: antidepressant, gastrointestinal bleeding, NSAID, aspirin

Introduction
Medications that modulate serotoninergic neurotransmission, like selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), are commonly prescribed to treat depression, anxiety disorders, and premenstrual dysphoria, as well as chronic pain conditions. During the past decade, numerous reports have been published on the risk of abnormal gastrointestinal (GI) bleeding as an infrequent adverse event (AE) associated with serotonin-modulating drugs. Patients with musculoskeletal pain conditions, as well as patients with depression and anxiety who experience chronic pain, may also be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin, which are also associated with GI bleeding. Concomitant use of NSAIDs with SSRIs or SNRIs may potentiate bleeding-related AEs.

The tendency for GI bleeding during treatment with serotonin-modulating drugs is linked to a decrease in blood platelet function that is dependent on serotonin. Platelets release serotonin at sites of vascular injury, which signals vasoconstriction and amplification of platelet aggregation for hemostatic thrombus formation. However, platelets accumulate serotonin via transporters. Treatment with therapeutic doses of serotonin-modulating agents blocks these transporters, ultimately impairing serotonin accumulation and thereby rendering platelets dysfunctional.

Duloxetine (Cymbalta; Eli Lilly and Company, Indianapolis, IN, USA) is an SNRI that is approved by the US Food and Drug Administration (FDA) for the treatment of major depressive disorder and generalized anxiety disorder and the management of neuropathic pain associated with diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain associated with osteoarthritis and chronic low back pain. Outside of the United States, it is also approved for lower urinary tract disorders in some countries. A safety profile of duloxetine across these indications has been published that analyzed rates of common treatment-emergent AEs (TEAEs) (defined as AEs that were experienced by 5% or more of duloxetine-treated patients) comparing duloxetine with placebo. In those analyses, the frequency of any single bleeding-related event did not meet the threshold for being classified as a common TEAE. The objective of the current analyses was to gain a better understanding of the risk of bleeding-related TEAEs associated with duloxetine treatment in patients who used concomitant NSAIDs. We analyzed the incidence of these TEAEs from placebo-controlled trials of duloxetine across indications. In addition, we analyzed the incidence of these events reported in the FDA Adverse Event Reporting System (FAERS), which receives reports from health care professionals, consumers, and pharmaceutical manufacturers.

Methods
Characteristics of included studies
Safety data were pooled from all randomized, double-blind, placebo-controlled clinical trials of duloxetine conducted between December 1993 and December 2010. All studies were conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. National or institutional review boards at each study site approved the protocols, and written informed consent was obtained from each participant prior to entrance into a study. All patients were at least 18 years of age or older. The acute treatment phase duration of most studies was 3 months or less, and duloxetine doses ranged between 5 mg/day and 120 mg/day. Dosing schedules were fixed or flexible, and the majority of patients received 60 mg/day, 80 mg/day, or 120 mg/day. For all analyses apart from those examining the effect of dosing on bleeding outcomes, duloxetine dose groups were pooled.

Analysis of clinical trial data
Bleeding-related TEAEs were those events that newly occurred or worsened during the treatment phase as compared to the pre-randomization period. These events were coded into a preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 12.0, which could then be searched using preferred terms from the Standardized MedDRA Queries (SMQs [version 12.0]), that included hemorrhage non-laboratory terms (SMQ20000039) and hemorrhage laboratory terms (SMQ20000040). GI bleeding-related TEAEs were searched using specific GI bleeding-related preferred terms.

During each clinical trial, NSAID (including aspirin) use was recorded on electronic case report forms. The information on these forms lacked consistent comprehensive dose and/or duration of use, so concomitant NSAID use was defined as taking an NSAID at any time during the
treatment phase. Patients in both treatment groups were then categorized as an NSAID user or non-user.

Differences in the incidence of bleeding-related TEAEs between NSAID subgroups (user versus non-user) were analyzed by a logistic regression model that included therapy, NSAID use, and therapy-by-NSAID subgroup interaction. A statistically significant treatment-by-NSAID subgroup interaction was defined as \( P \leq 0.1 \). Within-subgroup group comparisons were conducted using Fisher’s exact test and were significant at \( P \leq 0.05 \).

To determine whether higher duloxetine doses were associated with an increased incidence of bleeding-related TEAEs, and also to assess if use of NSAIDs modify the dose effect of duloxetine, if such an effect exists, the 55 clinical trials were searched to identify fixed-dose studies with at least two fixed doses of duloxetine in the same study, allowing a direct comparison of two fixed-dose groups. Eight placebo-controlled clinical trials including fixed duloxetine doses of 60 mg, 120 mg, and placebo were found and analyzed. To examine for the presence or absence of a dose effect of duloxetine on the incidence of bleeding-related TEAEs, duloxetine 60 mg and 120 mg were compared with the Cochran–Mantel–Haenszel test for general association controlling for study. Furthermore, to evaluate if the use of concomitant NSAIDs modify the dose effect of duloxetine, if such an effect exists, a subgroup analysis was conducted using the same logistic regression model that included therapy, NSAID use, and therapy-by-NSAID subgroup interaction, with the exception that three treatment arms instead of two were examined.

Finally, to examine whether patients were exposed to a higher bleeding risk when taking duloxetine together with an NSAID compared with taking duloxetine on its own, the incidence of bleeding-related TEAEs was compared between NSAID user subgroups within treatment groups using the Cochran–Mantel–Haenszel test controlling for study.

**FAERS data analysis**

The FAERS database was searched through March 31, 2012 to ascertain whether there was disproportional reporting of bleeding-related TEAEs associated with duloxetine treatment and concomitant NSAID use (including aspirin). Bleeding-related TEAEs were combined into two groups based upon preferred terms SMQ (excluding laboratory terms). Upper GI bleeding events were combined into one preferred-term group, and another preferred-term group contained all other bleeding-related events. Among cases with duloxetine or NSAIDs as either suspected or concomitant drug(s), the following case groups were utilized: duloxetine without NSAIDs (duloxetine) and duloxetine + NSAIDs. A disproportionality analysis based on the empirical Bayes geometric mean (EBGM)\(^2\) was employed to analyze the case groups. The number of cases in the duloxetine group for each group of bleeding-related preferred terms was compared against the full FAERS background, which was comprised of the number of cases reported for each group of preferred terms for drugs other than duloxetine. A similar comparison was made for the number of cases in the duloxetine + NSAIDs group. In addition, the duloxetine + NSAIDs group was compared against the number of cases reported for each group of preferred terms for NSAIDs taken alone. The lower bound of a 90% confidence interval of EBGM (EB05) \( \geq 1 \) was used as the criterion to signify that the disproportionality of the number of cases reported were higher than in the comparison groups.

**Results**

**Placebo-controlled trials**

A total of 19,529 patients (duloxetine, \( N=11,305 \); placebo, \( N=8,224 \)) participated in 55 studies across duloxetine indications that included five studies in chronic musculoskeletal pain (three in chronic low back pain\(^{11–15} \) and two in osteoarthritis knee pain\(^{16,17} \)); four in diabetic peripheral neuropathic pain;\(^{18–21} \) five in fibromyalgia;\(^{22–26} \) four in generalized anxiety disorder;\(^{27–30} \) 20 in lower urinary tract disorder;\(^{31–44} \) and 17 in major depressive disorder.\(^{45–57} \) Across these trials among NSAID users, 2,580 received placebo and 3,357 received duloxetine; among NSAID non-users, 5,644 received placebo and 7,948 received duloxetine.

Bleeding-related TEAEs, including GI bleeding-related events, are summarized in Table 1. Overall, the proportion of duloxetine-treated patients experiencing at least one bleeding-related TEAE was significantly greater than that in placebo-treated patients (1.8% versus [vs] 1.2%; \( P=0.006 \)).

There was a significant treatment-by-NSAID-use subgroup interaction for the occurrence of at least one bleeding event \( (P=0.029) \), with a statistically significant duloxetine/placebo difference of 0.71% (1.51% vs 0.80%) in the NSAID non-user group as compared to a nonsignificant 0.22% difference (2.35% vs 2.13%) in the NSAID user group (Figure 1). This indicates the presence of a smaller duloxetine/placebo difference in patients taking concomitant NSAIDs compared with patients not taking NSAIDs. A significant treatment-by-subgroup interaction was not seen for the group of GI bleeding-related events, with a nonsignificant duloxetine/placebo difference of 0.08% (0.19% vs 0.11%) seen in the NSAID non-user group and a nonsignificant 0.10%
The dose analyses included eight fixed-dose studies across different disease states; within these studies, 930 patients were randomized to placebo, 913 to duloxetine 60 mg/day, and 904 to duloxetine 120 mg/day. Comparison of the incidence of bleeding-related TEAEs in patients treated with duloxetine 60 mg compared with duloxetine 120 mg revealed no statistically significant differences between the two dose groups for all-bleeding-related TEAEs combined or GI bleeding-related events only. For all-bleeding-related TEAEs combined, there was no statistically significant dose-by-NSAID interaction, indicating that use of NSAIDs did not modify the effect of duloxetine dose. For GI bleeding-related events, a dose-by-NSAID interaction could not be calculated because there were no events reported in at least one treatment arm in each of the NSAID user subgroups.

To examine whether patients were exposed to a higher bleeding risk when taking duloxetine together with an NSAID compared with taking duloxetine on its own,

**Table 1** Bleeding-related treatment-emergent adverse events that occurred in five or more duloxetine-treated patients overall and across NSAID user subgroups

<table>
<thead>
<tr>
<th>Bleeding-related adverse events</th>
<th>Duloxetine total N=11,305 n (%)</th>
<th>Placebo total N=8,224 n (%)</th>
<th>P-value</th>
<th>NSAID non-user</th>
<th>NSAID user</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duloxetine N=7,948 n (%)</td>
<td>Placebo N=5,644 n (%)</td>
<td>Within subgroup P-value</td>
<td>Duloxetine N=3,357 n (%)</td>
<td>Placebo N=2,580 n (%)</td>
</tr>
<tr>
<td>At least 1 event</td>
<td>199 (1.8)</td>
<td>100 (1.2)</td>
<td>0.006</td>
<td>120 (1.51)</td>
<td>45 (0.80)</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>8 (0.1)</td>
<td>4 (0.0)</td>
<td>0.425</td>
<td>5 (0.06)</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>32 (0.3)</td>
<td>18 (0.2)</td>
<td>0.521</td>
<td>19 (0.24)</td>
<td>10 (0.18)</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>5 (0.0)</td>
<td>0 (0.0)</td>
<td>0.073</td>
<td>3 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>5 (0.0)</td>
<td>5 (0.1)</td>
<td>0.575</td>
<td>3 (0.04)</td>
<td>2 (0.04)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>9 (0.1)</td>
<td>6 (0.1)</td>
<td>0.694</td>
<td>4 (0.05)</td>
<td>2 (0.04)</td>
</tr>
<tr>
<td>Bruising</td>
<td>14 (0.1)</td>
<td>4 (0.0)</td>
<td>0.096</td>
<td>8 (0.10)</td>
<td>1 (0.02)</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>28 (0.2)</td>
<td>19 (0.2)</td>
<td>0.901</td>
<td>20 (0.25)</td>
<td>8 (0.14)</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>15 (0.1)</td>
<td>6 (0.1)</td>
<td>0.204</td>
<td>11 (0.14)</td>
<td>3 (0.05)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>5 (0.0)</td>
<td>1 (0.0)</td>
<td>0.199</td>
<td>3 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>Rectal hemorrhage</td>
<td>11 (0.1)</td>
<td>5 (0.1)</td>
<td>0.346</td>
<td>7 (0.09)</td>
<td>3 (0.05)</td>
</tr>
<tr>
<td>Vaginal hemorrhage</td>
<td>16 (0.1)</td>
<td>8 (0.1)</td>
<td>0.400</td>
<td>9 (0.11)</td>
<td>5 (0.09)</td>
</tr>
</tbody>
</table>

**Figure 1** Percentage of patients in the nonsteroidal anti-inflammatory drug (NSAID) user/non-user subgroups that reported any treatment-emergent bleeding-related adverse event during placebo-controlled trials of duloxetine.

**Notes:** NSAID non-user group versus NSAID user group, P<0.001. Treatment-by-subgroup interaction, P=0.029.
statistical comparisons were conducted for the comparison of duloxetine + NSAID versus duloxetine alone, as well as the comparison of placebo + NSAID versus placebo alone. Regarding all bleeding-related TEAEs, 2.35% of duloxetine-treated patients who used concomitant NSAIDs experienced a bleeding-related event versus 1.51% of duloxetine-treated patients who did not take an NSAID ($P<0.044$), while 2.13% of placebo-treated patients who also took an NSAID experienced a bleeding-related event versus 0.8% of patients treated with placebo alone. The incidence of GI bleeding-related events within treatment groups was not statistically significantly greater for NSAID users compared with non-users. In duloxetine-treated patients, 0.33% of NSAID users versus 0.19% of NSAID non-users ($P=0.536$) experienced a GI bleeding-related event, and in placebo-treated patients, 0.23% of NSAID users versus 0.11% of NSAID non-users ($P=0.488$) experienced a GI bleeding-related event.

**FAERS**

Cases for the all-bleeding-related TEAEs and upper GI bleeding-related TEAEs are summarized in Table 2. The results of the disproportionality analysis for these events are shown in Table 2 and Figure 3. None of the bleeding events, including upper GI bleeding events, were disproportionally reported for duloxetine monotherapy when compared against the full FAERS background that included cases for all other drugs. The reporting of the all-bleeding-related events group (EB05=1.31) and the upper GI bleeding group (EB05=1.12) was more frequent in the cases reported for duloxetine taken with NSAIDs than in the cases reported for drugs other than duloxetine. However, there was no difference in reporting of

Table 2 Bleeding events from the FAERS up to March 31, 2012 and the results of disproportionality analysis

<table>
<thead>
<tr>
<th>Case groups</th>
<th>Group of preferred terms</th>
<th>Cases for duloxetine</th>
<th>Cases for all other drugs</th>
<th>EB05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine on the full FAERS drugs background</td>
<td>All bleeding events</td>
<td>1,112</td>
<td>345,876</td>
<td>0.63</td>
</tr>
<tr>
<td>Duloxetine + NSAIDs on the full FAERS drugs background</td>
<td>Upper GI bleeding</td>
<td>116</td>
<td>57,307</td>
<td>0.36</td>
</tr>
<tr>
<td>Duloxetine + NSAIDs on the full FAERS NSAIDs background</td>
<td>All bleeding events</td>
<td>504</td>
<td>346,484</td>
<td>1.31</td>
</tr>
<tr>
<td>Duloxetine + NSAIDs on the full FAERS NSAIDs background</td>
<td>Upper GI bleeding</td>
<td>80</td>
<td>57,343</td>
<td>1.12</td>
</tr>
<tr>
<td>FAERS NSAIDs drugs background</td>
<td>All bleeding events</td>
<td>504</td>
<td>74,397</td>
<td>0.75</td>
</tr>
<tr>
<td>FAERS NSAIDs drugs background</td>
<td>Upper GI bleeding</td>
<td>80</td>
<td>25,892</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Abbreviations: FAERS, US Food and Drug Administration Adverse Event Reporting System; EB05, the lower bound of 90% confidence interval of empirical Bayes geometric mean; GI, gastrointestinal; N, total number in group; NSAIDs, nonsteroidal anti-inflammatory drugs.
either group of events when the cases reported for duloxetine taken with NSAIDs were compared against the cases reported for NSAIDs without duloxetine.

**Discussion**

To our knowledge, this is the first study to investigate GI and other bleeding-related TEAEs that may be associated with a single SNRI, duloxetine, when taken concomitantly with, and without, NSAIDs. Previous studies have reported on serotonin reuptake inhibitors as a class (SSRIs or SNRIs or both classes combined)\(^5\,^5\,^8\,\text{--}\,^6\,^2\) without regard to individual differences among these medications with respect to their affinity for the serotonin reuptake receptor, which may affect the level of risk for bleeding-related TEAEs when taken alone or in combination with NSAIDs.\(^6\,^3\,\text{--}\,^6\,^4\)

Consistent with duloxetine’s mechanism of action, more duloxetine-treated patients in clinical trials experienced a bleeding-related AE compared with placebo-treated patients. A significantly greater risk of bleeding-related events was seen among duloxetine- versus placebo-treated clinical trial patients who did not use NSAIDs; interestingly, however, while rates of bleeding-related TEAEs were higher in both the duloxetine and placebo treatment groups in patients who also took concomitant NSAIDs, the duloxetine/placebo difference in these rates was smaller than that in the NSAID non-user group and not statistically significant. We hypothesize that the bleeding risk associated with NSAID treatment is greater than that of duloxetine alone, thereby diluting the duloxetine/placebo difference when duloxetine is combined with NSAIDs. These results do not indicate that the combination of duloxetine and NSAIDs significantly increases the bleeding risk beyond the individual risks of each agent.

There was no statistically significant difference between the duloxetine 60 mg and 120 mg doses with respect to the incidence of either all-bleeding-related events or GI bleeding-related events. While this suggests that the use of higher doses of duloxetine is not associated with an increased risk of bleeding events, the results should be interpreted with caution, as relatively few patients were included in the analyses due to the need to include studies with at least two fixed duloxetine-dose arms and a placebo control. There were no duloxetine dose-by-NSAIDs interactions to suggest that the use of concomitant NSAIDs might influence the effect of duloxetine dose.

To address the question of whether patients are exposed to a higher bleeding risk when taking duloxetine together with NSAIDs compared to taking duloxetine alone, between-subgroup comparisons were conducted within treatment groups. The combination of duloxetine and NSAIDs was associated with a statistically significantly higher incidence rate of all bleeding TEAEs compared with duloxetine alone, suggesting an increased risk of bleeding with the combination. Given the well-known risks of bleeding associated with NSAIDs, the finding of a greater incidence of bleeding events for the combination of duloxetine and an NSAID compared with duloxetine alone seems unsurprising. It must, however, be remembered that patients were not randomly assigned to take duloxetine plus NSAIDs or duloxetine alone, so the finding should be treated with caution due to the potential for selection bias.
The results of the disproportionality analysis of bleeding events reported in the FAERS were not significant based on a conservative threshold of $\text{EB}_05 \geq 1.0$ when duloxetine cases, without NSAIDs as suspected or concomitant drugs, were compared with cases reported for all other drugs. Disproportional reporting was found when duloxetine cases with NSAIDs as suspected or concomitant drugs were compared to cases reported for all other drugs, excluding duloxetine and NSAIDs. However, the disproportionality of reporting for these events disappeared when compared to cases reported for NSAIDs taken alone, suggesting that the finding was driven by concomitant NSAID use rather than by duloxetine. These results are supported by other researchers who did not find an increased risk for bleeding events when NSAIDs were taken with SSRIs, especially when compared to the risk of taking NSAIDs alone.\textsuperscript{64,65}

There are limitations to the analyses of placebo-controlled data. First, the clinical trial data are limited by incomplete information regarding dosing and frequency of concomitant NSAID use. Because of this challenge, we were unable to discern whether patients were taking a therapeutic dose every day or less frequently during the study. Based on what is known about the risk factors for bleeding events, these scenarios could have very different risks. The short duration of most of these studies may also limit the occurrence and detection of bleeding events that develop with prolonged concomitant NSAID use. Regarding the dose analyses, the results should be interpreted with caution – relatively few patients were included in the analyses due to the need to include studies with at least two fixed duloxetine-dose arms and a placebo control.

It is also important to understand the limitations of analyses based on the FAERS data. The rate of spontaneous reporting of any selected TEAE may not reflect the true incidence of that event in the population due to recognized underreporting of these events. In addition, the analyses based on spontaneous datasets like the FAERS are also hampered by duplicate case listings and a large number of false-positive results.

**Conclusion**

Duloxetine-treated patients in clinical trials had a higher incidence of bleeding-related TEAEs compared with placebo-treated patients, although the duloxetine/placebo difference was smaller in patients using concomitant NSAIDs than it was in non-NSAID users; concomitant use of NSAIDs was associated with a higher incidence of bleeding-related TEAEs in clinical trial patients regardless of whether they were taking duloxetine or placebo. Use of a higher (120 mg once daily) dose of duloxetine was not associated with a higher incidence of bleeding-related events than a lower (60 mg once daily) dose, regardless of concomitant NSAID use; the dose analyses should, however, be treated with caution due to the small sample size. The combination of duloxetine and NSAIDs was associated with a statistically significantly higher incidence rate of all bleeding TEAEs compared with duloxetine alone, suggesting an increased risk of bleeding with the combination. In spontaneously reported post-marketing data, duloxetine and concurrent NSAID use was not associated with significant disproportional reporting of bleeding events when compared with NSAID use alone.

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**Disclosure**

All authors own stock in and are employees of Eli Lilly and Company or a subsidiary. The authors report no other conflicts of interest in this work.

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