CHAPTER 6

Is combined use of SSRIs and NSAIDs associated with an increased risk of starting peptic ulcer treatment? Reanalysis of a cohort study using a prescription sequence symmetry design

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Abstract

Background
A Dutch cohort study reported that the combined use of SSRIs with NSAIDs synergistically increases the risk of initiating a treatment course with peptic ulcer drugs (used as a proxy for uncomplicated gastrointestinal adverse effects) compared to TCA users. However that study was prone to unmeasured confounding, as no adjustment for potential differences between SSRI and TCA users was performed. We evaluated the same association in the same database using a prescription sequence symmetry analysis.

Methods
Drug dispensing data between 1994 and 2011 were retrieved from the IADB.nl database. A prescription sequence symmetry analysis was used to assess whether peptic ulcer drugs were prescribed more often following SSRI therapy initiation in combination with NSAIDs, than the other way around. The association between NSAIDs alone and peptic ulcer drugs was also evaluated, as a positive control.

Results
In total, 50,350 incident SSRI users were identified. Of these patients, 277 were incident users of both SSRIs and peptic ulcer drugs within a four week time-span. Less patients received peptic ulcer drugs after SSRI therapy initiation than the other way around (126 vs. 151), corresponding to an adjusted sequence ratio (ASR) of 0.83 (95% confidence interval [CI] 0.65-1.06). The ASR of concurrent use of SSRIs and NSAIDs (1.48, 95% CI, 0.90-2.49) did not exceed the ASR of NSAIDs alone (2.50, 95% CI, 2.27-2.76).

Conclusions
Our findings indicate that at least part of the previously reported association between combined use of SSRIs with NSAIDs and peptic ulcer initiation might be attributed to unmeasured or residual confounding.
Introduction

Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressant drugs that are thought to increase the risk of gastrointestinal adverse events [1]. De Jong et al., reported that the combined use of nonsteroidal anti-inflammatory drugs (NSAIDs) with SSRIs synergistically increased the risk of initiating a treatment course with peptic ulcer drugs as a proxy for gastrointestinal adverse effects (RR 12.4, 95% CI 3.2-48.0). In an attempt to limit confounding by indication, tricyclic antidepressant (TCA) users were used as a control group. As the observed association was not adjusted for potential differences between TCA and SSRI users [1], channelling bias or unmeasured confounding may have affected the estimation of the adverse effects.

We re-analysed the study of De Jong et al. [1] to evaluate whether the dramatic increased risk associated with combined use of SSRIs and NSAIDs could be (partly) explained by differences in patient characteristics between SSRI and TCA users.

A prescription sequence symmetry analysis was used to overcome the problem of finding an appropriate control group. The main advantage of this method is that the patient population serves as its own control group, thereby controlling for time-invariant (unmeasured) confounding.

Methods

A prescription sequence symmetry analysis was applied to data from the same pharmacy prescription database (IADB.nl) that de Jong et al. [1] used. This database contains prescription data from 1994 till 2011 from approximately 54 Dutch community pharmacies and covers an estimated population of 500,000 patients [2]. The database has been shown to be representative for the Netherlands in terms of drug use [3]. The database contains, among other data, information on the date of prescription, number of days the drug was prescribed for and the number of prescribed daily doses based on the WHO definition [2]. The medication records for each patient are virtually complete, except for over the counter (OTC) drugs and medication dispensed during hospitalization [4].

Study population and outcome definition

From the IADB.nl database incident users of SSRIs (Anatomical Therapeutic Chemical classification [ATC] code N06AB), TCAs (ATC code N06AA), NSAIDs (ATC code
M01A) and peptic ulcer drugs (ATC code A02B) were selected. Only people who were 18 years or older during the first incident prescriptions were included.

Incident users of a drug were defined as users who did not use the drug in a period of 6 months before the first prescription, while being captured in the database for at least that period of time. All patients being prescribed thrombocyte aggregation inhibitors (ATC code B01A) or systemic corticosteroids (ATC code H02) in a period of 6 months before the incident use of the above mentioned drugs (SSRIs, TCAs, NSAIDs and peptic ulcer drugs) were excluded. The outcome was defined as a first start of a peptic ulcer drug course (H$_2$-receptor blocking agents, proton pump inhibitors, prostaglandins [ATC code A02B]).

**Statistical analysis**

A prescription sequence symmetry analysis was performed to evaluate whether peptic ulcer drugs were prescribed more often following the drugs of interest than the reverse [5]. When assessing the association between initiating treatment A and B, the sequence ratio (SR) is calculated by dividing the number of individuals starting treatment A first and treatment B second by the number of individuals starting treatment B first and treatment A second. If there would be no association between the drugs, patients should have equal probabilities to receive the drugs in either order, yielding a SR of 1. However if drug A has a side-effect that is treated with drug B, more patients would be prescribed drug B after drug A than the reverse, yielding a SR above 1.

Since prescription sequence symmetry analyses are vulnerable to trends in prescribing, we adjusted the crude SR for time trends in use of the study drugs. The adjusted SR was obtained by dividing the crude SR by a null ratio, i.e. the SR obtained assuming no association between both drugs based on overall prescribing of both drugs in the total IADB population, taking into account the exclusion criteria [5, 6]. For concurrent use of NSAIDs and SSRIs or TCAs we used the null-ratios obtained for NSAIDs alone. The adjusted SR is an estimate of the incidence ratio of peptic ulcer prescribing in exposed versus non-exposed person time [5, 6].

For the primary analysis, only patients for which the time-span between both incident prescriptions was between 2 and 28 days were included to limit time-varying confounding. We estimated 95% confidence intervals (95% CIs) of SRs using exact confidence intervals for binomial distributions using STATA 12 software (StataCorp LP, College Station, TX, USA).
**Sensitivity analyses**

In sensitivity analyses we evaluated whether our results were sensitive to certain choices in the design. First, because knowledge about a possible side-effect might influence the prescribing of general practitioners, we assessed whether restricting our analyses to the period before July 2000, the cut-off date De Jong et al. used [1], would change our results. Second, we evaluated the effect of using a drug-free run-in period of two years instead of half a year. Third, we calculated the ASR for SSRI and peptic ulcer drugs within different time-spans to evaluate whether the possible association would be stable using different time-windows ranging from two to eight weeks. Fourth, we evaluated whether excluding individuals using ATC code ‘M01AX’ (Other anti-inflammatory and anti-rheumatic agents, non-steroids) influenced the results. Finally, we restricted our analyses to patients that started with SSRI therapy within 90 days before the first NSAID prescription to exclude patients that already used SSRIs for a long period, before their first NSAID prescription.

**Results**

In total, 50,350 incident adult patients who initiated SSRI treatment were identified between July 1994 and December 2011. The median age of these patients at the start of SSRI therapy was 43 [interquartile range (IQR), 25], 64.0% was female and 25.8% had recorded use of NSAIDs in the year prior to SSRI therapy initiation. After excluding patients that used peptic ulcer drugs within 1 day of SSRI therapy initiation and those that used NSAIDs, systemic corticosteroids or thrombocyte aggregation inhibitors, 277 patients that received a peptic ulcer drug course within 4 weeks prior to or after SSRI treatment initiation were identified. The median age of these patients at the start of SSRI treatment was 42 (IQR 23) and 61.7% was female.

Of these 277 patients, 126 (45%) started SSRI therapy prior to peptic ulcer drug treatment, while 151 (55%) patients started peptic ulcer drug treatment first, which corresponds to an adjusted sequence ratio of 0.83 (95% CI, 0.65-1.06) (Table 6.1).

Concurrent use of SSRIs and NSAIDs was associated with a statistically non-significant increase in the risk of starting peptic ulcer drug treatment (aSR, 1.48, 95% CI 0.90-2.49), which did not exceed the risk estimated for NSAID treatment alone (aSR 2.50, 95% 2.27-2.76). Similar results were obtained for TCA treatment alone and concurrent use of TCAs and NSAIDs (Table 6.1).
Table 6.1. Symmetry analysis of selected drug therapy initiation within 4 weeks of peptic ulcer drug therapy initiation using a drug-free run-in period of half a year.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peptic ulcer drug prescribed first/second (n)</th>
<th>Adjusted sequence ratio (95% CI)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>151/126</td>
<td>0.83 (0.65-1.06)</td>
</tr>
<tr>
<td>NSAID</td>
<td>571/1445</td>
<td>2.50 (2.27-2.76)</td>
</tr>
<tr>
<td>SSRI+NSAID</td>
<td>28/42</td>
<td>1.48 (0.90-2.49)</td>
</tr>
<tr>
<td>TCA</td>
<td>68/63</td>
<td>0.92 (0.65-1.32)</td>
</tr>
<tr>
<td>TCA+NSAID</td>
<td>11/16</td>
<td>1.44 (0.63-3.43)</td>
</tr>
</tbody>
</table>

\(^a\) adjusted for trends in prescribing

**Sensitivity analysis**

Restricting the analysis to data obtained before the end of the study period of De Jong et al. [1], did not substantially change the results. No association was found between SSRIs and peptic ulcer drug initiation (aSR 0.85, 95% CI 0.54-1.33), while an association between NSAIDs and peptic ulcer drugs was still present (ASR 1.91, 95% CI 1.61-2.29). In addition, the risk of concomitant use of NSAIDs and SSRIs was still not higher than the risk for NSAIDs alone.

The results were insensitive to prolonging the drug-free run-in period from half a year to two years. Using this prolonged run-in period, no association was found between SSRIs and peptic ulcer drugs (ASR 0.98, 95% CI 0.74-1.30). Additionally, the sequence ratio for concomitant use of NSAIDs and SSRIs (aSR 1.38, 95% CI 0.75-2.59) remained lower than for NSAIDs alone (aSR 2.96, 95% CI 2.61-3.36).

When using different maximum time-spans between both first prescriptions, ranging from 1 to 8 weeks, no association was present between SSRIs and peptic ulcer drugs. The sequence ratios were relatively stable within these different maximum time-spans between the prescriptions, ranging from an aSR of 0.87 (95% CI 0.70-1.09) to 1.00 (95% CI 0.73-1.37). The results for concomitant use of NSAIDs and SSRIs were also
relatively stable using these different time-spans, ranging from an aSR of 1.24 (95% CI 0.76-2.12) to 1.67 (95% CI 0.88-3.35).

Excluding individuals using ATC code ‘M01AX’ did not change the results, as none of the patients receiving a first peptic ulcer drug course within 28 days of starting with concomitant use of NSAIDs and SSRIs did use a drug that falls in this category.

When restricting our analyses to patients that started with SSRI therapy within 90 days before the first NSAID prescription, the aSR was not higher for concurrent use of SSRIs and NSAIDs than for NSAIDs alone using both a run-in period of half a year (2.23 vs 2.50) and a run-in period of 2 years (1.32 vs 2.96).

Only 3 patients initiated SSRI and NSAID therapy on the same day, without receiving prophylactic peptic ulcer drugs. Two patients received first this combination of drugs and then peptic ulcer drugs, while one patient received those drugs in the reverse order.

**Discussion**

This prescription sequence symmetry analysis suggests that concurrent use of SSRIs and NSAIDs is not associated with an increased risk of starting peptic ulcer treatment compared to NSAIDs alone. Our results are in contrast with the study of De Jong et al. who found that combined use of NSAIDs with SSRIs synergistically increased the risk of initiating a treatment course with peptic ulcer drugs.

Given that we used the same database and similar inclusion and exclusion criteria as de Jong et al. [1], the main difference between their study and ours is that we used an alternative design that reduces time-invariant (unmeasured) confounding. In accordance with our results, Dall et al., who applied a case-control design in which they controlled for various potential confounders including alcohol abuse, did not observe an increased risk of uncomplicated peptic ulcers associated with combined use of SSRIs and NSAIDs [7]. These data suggest that the synergistically increased risk of combined use of SSRIs and NSAIDs found by De Jong et al. [1], might be, at least partly, contributed to unmeasured confounding. The study of De Jong et al. was vulnerable to confounding bias, because they compared SSRI users with TCA users, without adjusting for any potential differences between these different types of patients [1].

For example, it has been shown that heavy alcohol use is a strong confounder when evaluating the association between SSRI use and GI bleeding [8]. This can be explained by the fact that alcohol abuse is a well-known risk factor for both GI adverse events and
depression. TCAs can potentiate the effects of alcohol due to their antihistaminic effects, while SSRIs have minimal antihistaminic properties [9] and consequently do have minimal effects on alcohol pharmacokinetics and pharmacodynamics [10]. Therefore, alcohol abuse might be less common among TCA users than among SSRI users, due to channelling by the physician. In our database, SSRI users were indeed approximately 2 times more likely to use drugs indicated for treatment of alcohol dependence (ATC code N07BB) than TCA users.

The main strength of our study is that we controlled for time-invariant (unmeasured) confounding, because the patient population serves as its own control. By using relatively short time-spans between SSRI and peptic ulcer drug prescriptions we further reduced (unmeasured) time-varying confounding.

However, the prescription sequence symmetry analysis is still vulnerable to confounding by disease severity or sudden-onset diseases. Despite figure 1 suggests that confounding by disease severity or other time-varying variables might result in spurious inflations of the risk of starting peptic ulcer treatment; we did not find an increased risk associated with SSRIs, indicating that our results are not largely affected by changes in disease severity.

Alternatively, it is possible that we could not detect an increased risk using our study design, because we could not capture peptic ulcer drugs courses prescribed during hospitalizations or measure over-the-counter NSAID and peptic ulcer drug use. However, De Jong et al. did previously find and increased risk in patients concurrently using SSRIs and NSAIDs, while coping with the same limitations [1]. Moreover, the well-known increased risk of gastrointestinal adverse effect after starting with NSAID treatment [11, 12] was conformed in our study. Therefore, the lack of an increased risk associated with SSRI use, whether or not used concurrently with NSAIDs, is likely not related to these potential limitations.

It is possible that using a drug-free run-in period of half a year was not long enough to guarantee incident use of the study-drugs. We used a run-in period of half a year as we tried to use the same restrictions as De Jong et al. did [1], to be able to make a fair comparison. However, sensitivity analysis showed that prolonging the drug-free run-in period to two years did not substantially change the SR estimates.

While De Jong et al. assessed the effect of concurrent use of NSAIDs and SSRIs in starters [1], we assessed the effect of co-administration of NSAIDs in more chronic SSRI users. Because patients that experience adverse events with SSRIs may self-select
themselves out of longer treatment [13], starters might have a different risk than chronic SSRI users. However, restricting our analyses to patients that started with SSRI therapy within 90 days before the first NSAID prescription did not substantially change the SR estimates.

As we restricted our analyses to relatively short time-spans to reduce the potential influence of time-varying confounding, we could not detect a risk that develops later in the course of treatment. However, De Jong et al. found an increased risk for concomitant use of SSRIs and NSAIDs during an average follow-up of 21 days [1]. In addition, Dall et al. found that the risk of uncomplicated peptic ulcers is strongest during the first 30 days of SSRI treatment [7], indicating that our time-span of four weeks should be long enough to capture potential drug-related increases in peptic ulcer drug prescribing.

In conclusion, our results suggest that the observations reported by de Jong et al. [1] might, at least partly, be attributed to unmeasured confounding. Although comparison with a drug that is used to treat the same indication does limit confounding, it does not eliminate all potential confounders. Therefore, when limited data on potential confounders are available, a self-controlled design can have added value, because it reduces time-invariant confounding [14].
References


