

Impact of a national Smarter Medicine guideline on outpatient proton-pump inhibitor prescription in Switzerland: a nationwide interrupted time-series analysis

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Summary

BACKGROUND: Proton-pump inhibitors (PPI) are a key treatment for gastro-oesophageal disease, but their frequent overprescription leads to potential adverse effects and an economic burden. In this retrospective study, we investigated the effect of a Smarter Medicine guideline published in May 2014 by the Swiss Society of General Internal Medicine, which recommended that general practitioners should avoid "long-term treatment of gastrointestinal symptoms with proton-pump inhibitors without titrating to the lowest effective dose needed".

METHODS: An interrupted time-series analysis was performed using a Seasonal AutoRegressive Integrated Moving Average (SARIMA) model, which was validated through a Bayesian Model Averaging algorithm with changepoint detection. National PPI sell-in data was provided by IQVIA and covered 100% of oral and intravenous PPIs distributed in Switzerland from 2009 to 2019. The main outcome was the monthly number of oral PPI defined daily doses (DDD) per 100,000 inhabitants aged ≥ 20 years. A regression analysis was conducted to estimate pre-guideline trend, post-guideline level change and post-guideline slope change. Using Bayesian Model Averaging, the probability of changepoint occurrence over time was calculated without predetermined intervention dates. Oral PPI DDDs were used as a surrogate for outpatient prescriptions, while intravenous PPI DDDs served as a control in Bayesian Model Averaging.

RESULTS: Following guideline publication, a significant post-guideline downward trend of oral PPI DDDs was observed (slope change, $p < 0.001$). Bayesian analysis of oral PPI DDDs supported a single changepoint with 92% probability, most likely occurring within 2 years after guideline publication (79% summed changepoint occurrence probability). For intravenous DDDs, the probability of a single changepoint dropped to 41%, with only 29% summed probability for the same period.

CONCLUSIONS: A significant downward trend in PPI oral DDDs was observed after the Smarter Medicine guideline publication, suggesting that primary care guidelines have the potential to induce change in prescribing behaviour.

Introduction

Proton-pump inhibitors (PPI) are a key treatment for gastrointestinal diseases like gastro-oesophageal reflux disease, stomach ulcers and upper gastrointestinal bleeding (or its prevention in certain circumstances), but prescriptions without indication or overly prolonged treatment durations remain common in ambulatory care [1-5]. Although PPIs are generally considered to have a good safety profile, observational data have shown an association with adverse events (fractures, hypomagnesaemia, iron and B12 deficiency, pneumonia and enteric infections), without a formal causality having been established yet [4, 5]. Despite these adverse events, a retrospective study in Switzerland based on a large insurance claims database concluded an increasing trend of inappropriate PPI prescriptions [6]. Furthermore, overprescription leads to an unnecessary economic burden on our health system. A recent assessment by the Swiss Federal Office of Public Health estimated that restricting reimbursement policy from continuous PPI therapy to on-demand PPI therapy could lead to savings of between CHF 50 and 127 million in 5 years [7]. To tackle these issues,

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numerous medical societies in different countries reinforce PPI deprescription in clinical practice [8, 9] but it remains unknown whether these guidelines have an effect on PPI prescription and consumption. In May 2014, the Swiss Society of General Internal Medicine issued a Top Five Smarter Medicine recommendations list for treatments or tests to be avoided in ambulatory care. One of the five recommendations was to avoid "Continuing long-term treatment of gastrointestinal symptoms with PPI without titrating to the lowest effective dose needed" [10, 11]. The present retrospective observational study aimed to evaluate the impact of the Smarter Medicine guideline on outpatient PPI prescription in Switzerland, using national oral PPI defined daily doses as a proxy for ambulatory prescribing.

Methods

Data source

Nationwide PPI sell-in data from pharmaceutical wholesale companies was provided by IQVIA Switzerland, a leading healthcare data company. The used sell-in data covered 100% of PPI medications distributed to pharmacies, self-dispensing doctors and hospitals in Switzerland from February 2009 to September 2019. The data provided by IQVIA consists of sell-in figures they receive monthly from wholesalers, physician suppliers, mail-order pharmacies, manufacturers and other purchasing organisations (100% coverage in Switzerland). All PPI molecules and doses available in Switzerland were included: dexlansoprazole (30 mg, 60 mg), esomeprazole (20 mg, 40 mg), lansoprazole (15 mg, 30 mg), omeprazole (10 mg, 20 mg, 40 mg), pantoprazole (20 mg, 40 mg) and rabeprazole (10 mg, 20 mg). In order to provide a standardised measurement unit, defined daily doses (DDD) were used in our study according to the NIPH (Norwegian Institute of Public Health, WHO Collaborating Centre for Drug Statistics Methodology): 30 mg/day for dexlansoprazole, esomeprazole and lansoprazole; 20 mg/day for omeprazole and rabeprazole; and 40 mg/day for pantoprazole [12]. Monthly PPI DDDs (per 100,000 inhabitants) were calculated using the annual Swiss population aged ≥ 20 years, as provided by the Swiss Federal Office of Statistics [13]. Data was separated into oral and intravenous medications. Oral PPI DDDs were used as surrogates for outpatient prescriptions, and intravenous PPI DDDs were used as controls for Bayesian Model Averaging (BMA), assuming that intravenous medication is not used for outpatients.

Main outcomes

The primary outcome was the monthly number of oral PPI DDDs per 100,000 inhabitants aged ≥ 20 years, used as a proxy for outpatient PPI prescriptions. Intravenous PPI DDDs were analysed as a control outcome for Bayesian Model Averaging analysis, assuming exclusive inpatient use.

Statistical model selection and validation

Interrupted time-series analysis was performed using a Seasonal AutoRegressive Integrated Moving Average (SARIMA) model with segmented regression terms and SARIMA errors. The regression component was used to estimate pre-guideline trend, immediate post-guideline level change and the post-guideline slope change. The SARIMA component was used to account for autocorrelation, moving-average error structure and annual seasonality in the residuals.

The SARIMA model was defined as:

$$Y_t = \beta_0 + \beta_1 * T_t + \beta_2 * D_t + \beta_3 * P_t + u_t$$

where Y_t represents monthly oral PPI DDDs, T_t is a continuous time variable in months, D_t is a binary variable before/after the guideline and P_t denotes time since guideline publication in months. Therefore, in this model β_1 estimates pre-guideline monthly trend, β_2 estimates the immediate post-guideline level change and β_3 estimates the change in monthly trend after guideline publication (slope change). The error term u_t was modelled as:

$$u_t \sim \text{SARIMA}(p, d, q)(P, D, Q)[S]$$

where (p), (d) and (q) denote the non-seasonal autoregressive, differencing and moving-average orders; (P), (D) and (Q) denote the corresponding seasonal orders; and (S) denotes the seasonal period [14].

Stationarity was assessed using the Augmented Dickey-Fuller test, which supported the use of $d=0$ ($p=0.03$). Seasonality (S) was chosen using the autocorrelation and partial autocorrelation plots (figure S1 in the appendix) which showed peaks every 6 and 12 months. After detrending the data, a peak every 12 months remained and $S=12$ was therefore chosen as seasonality. The other hyperparameters of the SARIMA model (p,q,P,D,Q) were determined using the *auto-ARIMA* package in Python. Competing models identified by minimisation of the Akaike information criterion (AIC), the Bayesian Information Criterion (BIC), the Hannan–Quinn information criterion (HQIC) and the Out-of-bag score (OOB) were compared using the Ljung-Box test and the normality tests. Since the lowest values for the model parameters (p,q,P,D,Q) were obtained by minimising the BIC, this minimisation criterion was applied, and the selected model was SARIMA(2,0,2)(1,0,0) [12]. The model was consistent with independent and normally distributed residuals (figure S2 in the appendix).

Statistical analysis

As the guideline was issued in May 2014, the data was split into a pre-guideline (64 months, February 2009 – May 2014) and a post-guideline group (64 months, June 2014 – September 2019). A regression analysis was conducted for the entire dataset of oral PPI DDDs using the SARIMA model, estimating pre-guideline trend, the immediate post-guideline level change and the post-guideline slope change. Level and slope changes were considered statistically significant for p -values <0.05 . Counterfactual post-guideline predictions were made with the SARIMA model using pre-guideline data only.

To validate the interrupted time-series analysis, a subsequent analysis by the Bayesian Model Averaging (BMA) algorithm was conducted. BMA accounts for model selection uncertainty by averaging multiple statistical models instead of selecting a single best model [15]. Most importantly, unlike interrupted time-series analysis, BMA does not presuppose an intervention. BEAST (Bayesian Estimator of Abrupt change, Seasonality and Trend) is a BMA model algorithm that can detect abrupt changes (i.e. changepoints) in time series and estimate their probability at any given point [16]. Using oral and intravenous DDDs, BEAST was used to calculate the probability of having zero, one or multiple changepoints (defined as dates where the statistical properties of the dataset change). Subsequently, the changepoint occurrence probability was calculated for each month, and the summed changepoint occurrence probability was calculated for the period from May 2014 to May 2016, corresponding to the 2 years after guideline publication.

The model validation and statistical analysis were conducted using Python (Python Software Foundation, Beaverton, USA) and are openly accessible on GitHub (GitHub Inc., San Francisco, USA) [17].

Results

The sell-in data included a total sale of over 2.3 billion pills and 6 million infusion bottles over 10 years. Pantoprazole was the most prescribed PPI, followed by esomeprazole and omeprazole (figure S3 in the appendix). In the interrupted time-series analysis, the estimated pre-guideline trend was an increase of 1335.6 oral PPI DDDs per 100,000 inhabitants per month (95% CI: 777.4–1893.9; $p < 0.001$). There was no significant immediate reduction of oral PPI DDDs after guideline publication: the estimated level change was 8535.2 oral PPI DDDs per 100,000 inhabitants (95% CI: -10600–27600; $p = 0.381$). However, the post-guideline oral PPI DDD trend was significantly reduced, with an estimated slope change of -1519.2 oral PPI DDDs per 100,000 inhabitants per month (95% CI: -2396.4–642; $p < 0.001$). The resulting post-guideline monthly trend, calculated as the sum of the pre-guideline trend and the slope change, was -183.5 oral PPI DDDs per 100,000 inhabitants per month. Therefore, the guideline was not associated with an immediate decrease in PPI DDDs, but a significant reduction of the previous increasing trend (figure 1 and table S4 in the appendix).

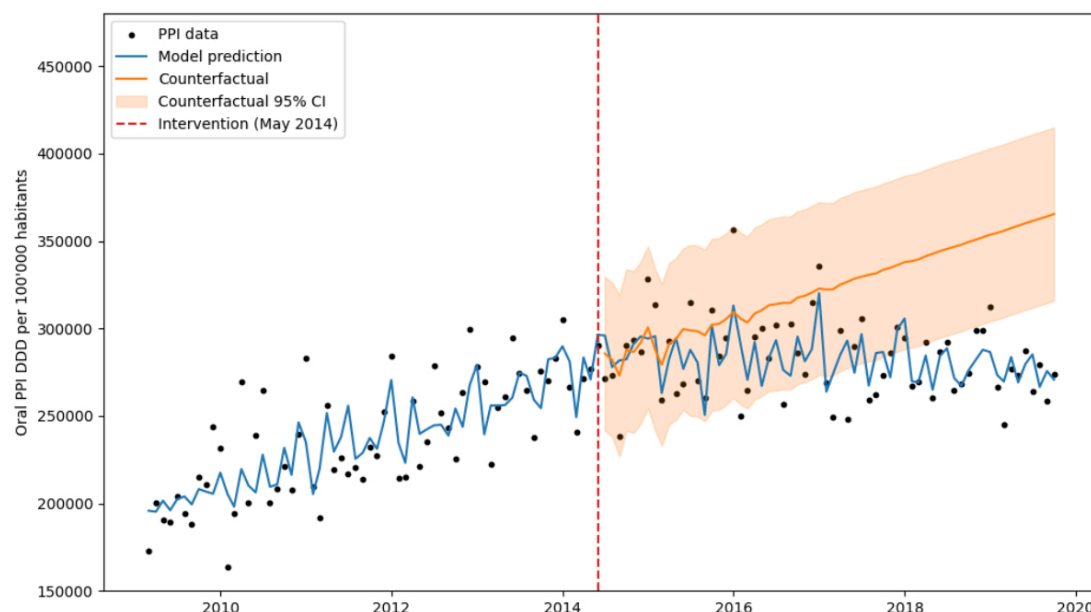


Figure 1: Oral proton-pump inhibitor (PPI) defined daily dose (DDD) rates over time. Blue: actual values fitted by the SARIMA model using pre- and post-guideline PPI data. Orange: counterfactual values fitted by the SARIMA model using only pre-guideline data. Shaded orange: 95% confidence interval.

Using the Bayesian model (BEAST) to detect changepoints without presupposing an intervention, we obtained only a probability of 3% for one or multiple seasonal changepoints. By contrast, we obtained a probability of 92% for a single trend changepoint (0% for no changepoint, 7% for 2 changepoints). Subsequently, assuming a single changepoint, we obtained a probability of 79% that the change occurred within 2 years of guideline publication (May 2014 – May 2016) (figure 2A).

Using intravenous PPI DDD as input for the Bayesian model, the probability for a single changepoint dropped to 41% while the probability for no changepoint increased to 29%. Even when assuming a single changepoint, we obtained a flat changepoint occurrence probability curve, and the summed probability for the period from May 2014 to May 2016 dropped to 29% (figure 2B).

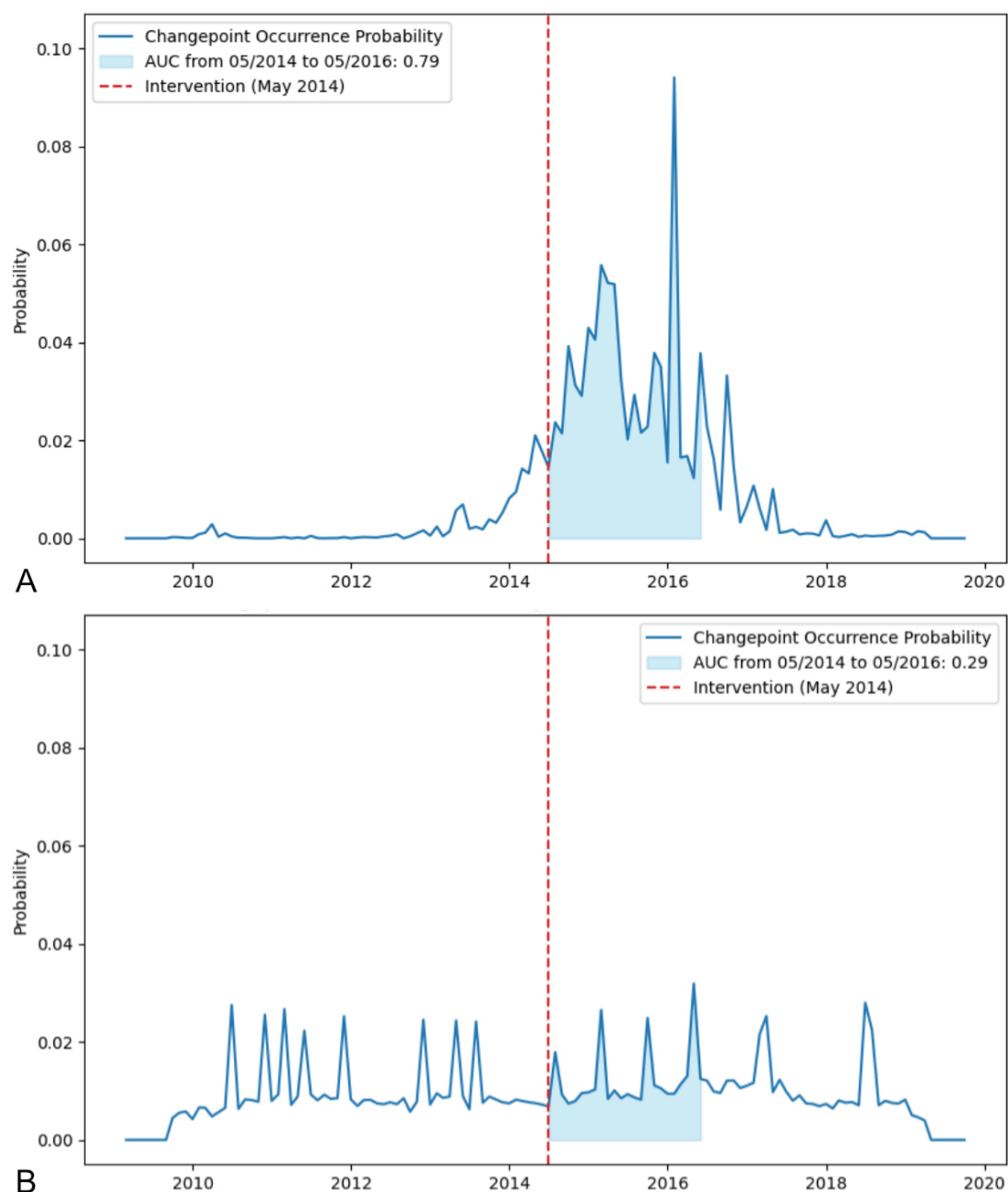


Figure 2: Changepoint occurrence probability over time, calculated by the Bayesian Model Averaging algorithm BEAST, for A) Oral and B) Intravenous proton-pump inhibitor (PPI) defined daily dose (DDD).

Discussion

Using a SARIMA model, this study demonstrated a significant downward trend (slope change) of oral PPI DDDs in Switzerland following the guideline publication. At the population level, we infer a similar trend change in outpatient PPI prescriptions. We validated the interrupted time-series analysis using a Bayesian analysis without presupposing the guideline issue date. Changepoint occurrence probability for oral PPI DDDs peaked at 1 to 2 years after the guideline publication, therefore accounting for the time needed by general practitioners to take notice of the guideline and review the medication of their patients at their next appointment. In contrast, Bayesian analysis of intravenous PPI DDDs supported absence of a changepoint. We therefore conclude that intravenous PPI prescriptions were not affected by the guideline. All these elements strongly support a causal link between the guideline and the downward trend of oral PPI DDDs.

Given that similar guidelines for PPI deprescription have been issued in other countries, other studies have been published about this topic. For instance, Abrahami et al. investigated the impact of NICE guidelines on PPI prescriptions in the United Kingdom but did not observe a significant change post-guideline implementation [18]. Since the guidelines were issued in the same year in both Switzerland and the United Kingdom, it is unlikely that the results of our study were influenced by a confounding bias on a European or global scale. However, one possible explanation for the discrepant findings between the UK and Switzerland is the different organisation of primary care. The NHS is mainly based on a pay-for-performance model, while the Swiss primary care system is predominantly financed by fee-for-service payments. In this setting, mean face-to-face consultations are as short as 10 minutes in the UK, while consultation times tend to be longer in Switzerland (around 15 minutes) [19]. As short consultation times represent one of the main barriers to deprescribing in primary care, different time constraints experienced by general practitioners could account for the discrepant study results.

Our findings are consistent with a study conducted in Australia, which examined the effect of two sequential guidelines in April 2015 and May 2016 on PPI use, based on dispensing records [20]. Despite a shorter follow-up period of only three years, the authors reported a 1.7% reduction in PPI dispensing. However, they did not observe significant changes in PPI discontinuation nor PPI dose switching.

While Muheim et al. have already provided evidence for rising and inappropriate PPI prescriptions in Switzerland [6], to our knowledge no study evaluating the impact of the Swiss Smarter Medicine PPI deprescription guideline has been published yet. Balafas et al. investigated the impact of a Smarter Medicine guideline on blood transfusion practices within a hospital network. They observed a decrease in inappropriate red blood cell transfusions with a changepoint almost two years after publication of the Swiss transfusion guidelines [21]. Our Bayesian analysis revealed approximately the same timeframe for the lag between guideline publication and its implementation.

Our study included a seasonal component to account for recurring calendar-related variation in monthly PPI DDD data. The Bayesian analysis did not provide evidence of a relevant change in this seasonal component before versus after guideline publication, suggesting that the observed post-guideline change was mainly attributable to a trend change rather than to altered seasonality. Potential explanations for recurring seasonal variation include calendar-related differences in patient consultations, prescribing or dispensing behaviour. Given that we used sell-in data and observed a yearly peak in December, part of this variation may also reflect year-end medication refills, possibly related to Swiss health insurance cost-sharing or deductible structures.

Future studies should clarify how PPI deprescribing can be implemented safely and effectively in primary care. As a matter of fact, lack of discussion about inappropriate PPI prescriptions and lack of time spent with each patient have been reported as the main barriers to reducing inappropriate PPI prescriptions in a Swiss primary care setting [22]. The ongoing Swiss DROPIT trial, a cluster-randomised controlled trial, is evaluating a structured deprescribing intervention for patients with inappropriate PPI treatment [23]. In this trial, the deprescribing intervention consists of deprescribing tools including educational material and decision aids for patients and general practitioners, as well as additional trainings for general practitioners. The outcomes will provide further evidence on how guideline recommendations can be translated into effective deprescribing practice.

The present study has several limitations. Firstly, the chosen measurement unit (oral PPI DDDs, calculated from PPI sell-in data) is an imprecise surrogate for inappropriate ambulatory PPI prescriptions. Even after excluding intravenous PPI, the provided data included both in- and outpatient prescriptions, while the guidelines target only the latter. We assumed that most long-term PPI prescriptions are made in ambulatory care, and that the proportion of hospital prescriptions is therefore negligible. In contrast, as deprescription consists both of dose reduction and medication cessation, by using DDD we also accounted for dose reduction effects in our study. Furthermore, as some molecules are available over-the-counter in Switzerland, sell-in data represents a more robust measurement than prescriptions for excluding the bias caused by patients simply switching to over-the-counter dispensing.

Given that pantoprazole is the most prescribed PPI molecule in Switzerland, the counterfactual post-guideline PPI DDD predictions may be largely driven by the rising pre-guideline pantoprazole PPI DDDs (figure S3 in the appendix). Nevertheless, as the Smarter Medicine guideline targets all outpatient PPI molecules, we decided to perform the statistical analysis on total PPI DDDs, only separating into oral and intravenous PPIs.

As our study setting was a retrospective observational population-based study, no conclusions can be drawn for individual patients. We did not measure clinical outcomes, and the impact on patient morbidity and mortality remains uncertain while this study does not show any evidence of clinical benefits or harm. However, a recent observational study conducted in the Swiss primary care setting showed a dose reduction or deprescription in 35% of inappropriate PPI prescriptions (roughly 10% of total PPI prescriptions) one year after flagging patients with inappropriate PPI prescriptions [22]. In our study, we cannot ascertain how effectively general practitioners targeted unnecessary PPI prescriptions, or whether patients with appropriate PPI use were also affected. A recent interventional study conducted using the US Veterans Affairs Healthcare System found that limiting PPI refills for patients without a documented long-term indication led to reduced overall PPI use, including among those appropriate for long-term use [24].

As is inherent to segmented regression models with SARIMA errors used for interrupted time-series analysis, the regressors T, D and P are mathematically correlated by construction, which may inflate standard errors of individual coefficients; this is reflected in the wide confidence interval observed for the level-change parameter (D; table S4 in the appendix). For this reason, we focused our interpretation on the slope-change parameter (P), which remained statistically significant despite this correlation structure.

Finally, in the absence of a true control population, we also cannot exclude the possibility of a confounding event around 2014. We searched for other guidelines issued at the same time but did not find any significant recommendations about PPI prescriptions. We accounted as much as possible for a numerical change in demographics (i.e. increasing Swiss population) while changes in patient characteristics (patient morbidity, increasing population age, disease incidence rates) were not considered. Furthermore, increasing use of direct oral anticoagulants, antiplatelet therapy, NSAIDs or corticosteroids may have influenced appropriate gastroprotective PPI use and represent a potential source of residual confounding. However, such factors would plausibly increase PPI use over time and may therefore have attenuated, rather than produced, the observed post-guideline reduction in trend. Despite the mentioned limitations of a retrospective study design, interrupted time-series analyses have been proposed as a robust study design for the retrospective evaluation of health system interventions [25].

Conclusion

This study demonstrated that a significant downward trend in PPI oral DDDs was observed after the Smarter Medicine guideline publication in May 2014. The interrupted time-series analysis was subsequently validated by the Bayesian Model Averaging algorithm, supporting a causal relationship between the guideline's introduction and this reduction. While their clinical benefit remains to be demonstrated, our study suggests that Smarter Medicine guidelines may have the potential to induce change in prescribing behaviour.

Data sharing statement

The analysed datasets are accessible on Github: <https://github.com/Flamanjaune/ppi-time-series-analysis/>

Notes

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Author contributions: DG and FP conceived the study. IQVIA provided the data, but were not involved in the study design, the statistical analysis or the manuscript writing. XR did the statistical analysis, helped by FP. FP and DB wrote the manuscript, DG and XR provided corrections and DG supervised the work. All authors read and approved the final manuscript.

Use of AI: The authors declare that generative artificial intelligence was used for spell-checking purposes only.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

SARIMA model calibration and validation

Figure S1:

Determination of SARIMA model seasonality hyperparameters using autocorrelation and partial autocorrelation plot. Figure 1 a) shows a decreasing trend with peaks every 6 months. After detrending the data to further discriminate between 6 or 12 months, Figure S1 b) shows a peak every 12 months, which was the time period chosen as seasonality.

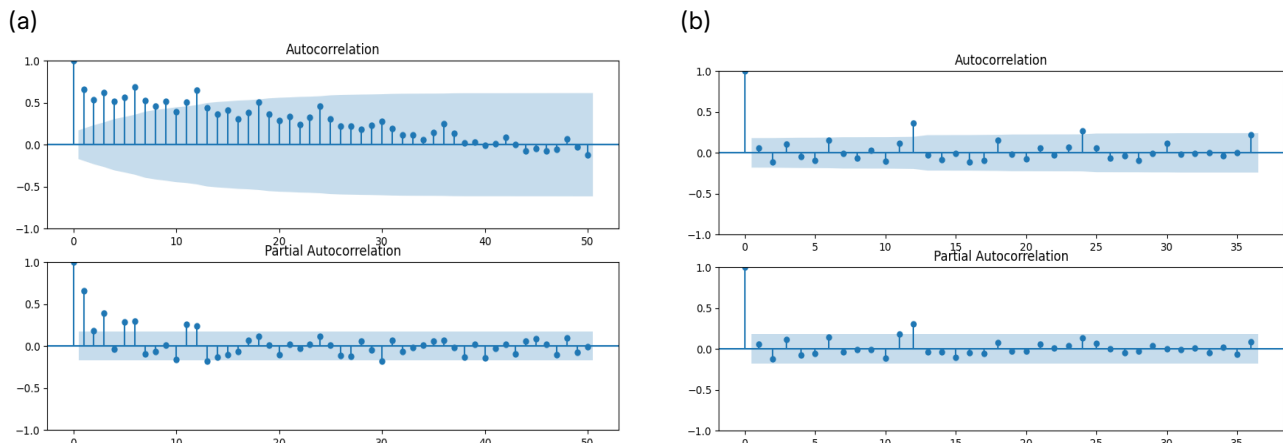
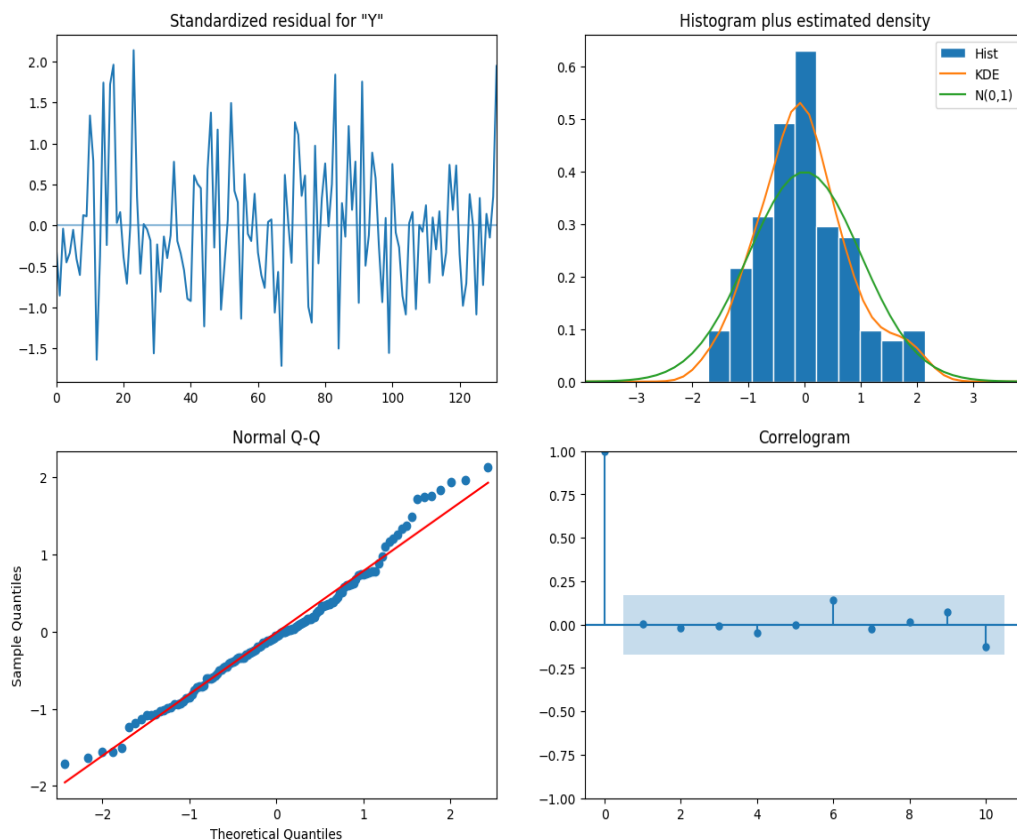


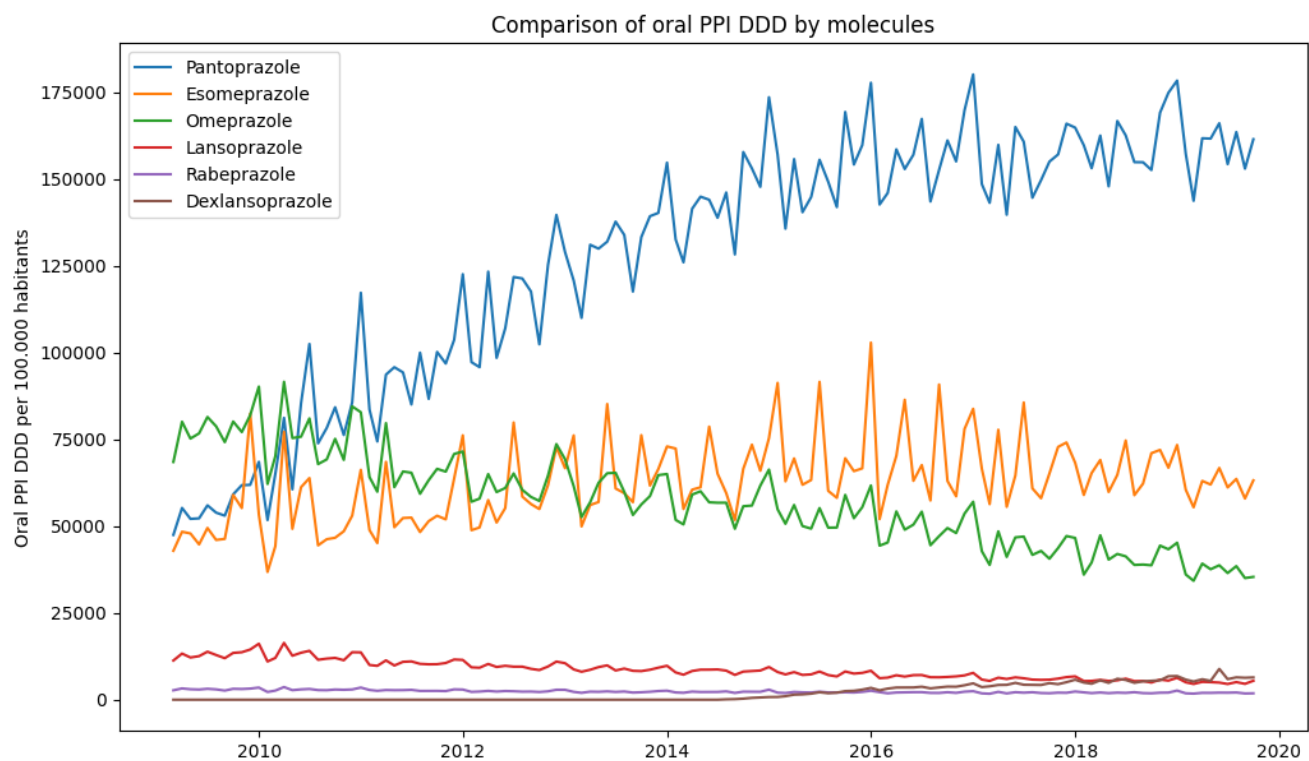
Figure S2:

The validity of the SARIMA model was checked using the Ljung-Box test (independently distributed residuals) and normality tests. No correlation in residuals was obtained (standardized residuals top-left and correlogram bottom-right plots). The residuals follow a normal distribution (histogram top-right and normal Q-Q bottom-left plots).



Comparison of Oral PPI DDD by molecules

Figure S3:
Monthly Oral PPI DDD per 100,000 habitants stratified by molecule



SARIMA Regression analysis

Table S4:
SARIMAX regression parameters for monthly oral PPI DDD per 100,000 inhabitants aged ≥ 20 years.

	Coefficient	Std error	p-value	95% CI
Constant	194,500	11,100	<0,001	173,000 to 216,000
T	1335.65	284.8	<0,001	777.4 to 1893.9
D	8535.15	9744.1	0.381	-10,600 to 27,600
P	-1519.17	447.6	0.001	-2396.4 to 642.0