

# Impact of EMA regulatory label changes on hydroxyzine initiation, discontinuation and switching to other medicines in Denmark, Scotland, England and the Netherlands: An interrupted time series regression analysis

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## Abstract

**Background:** Hydroxyzine is indicated for the management of anxiety, skin and sleep disorders. In 2015, the European Medicines Agency (EMA) concluded that hydroxyzine was pro-arrhythmogenic and changes to the product information were implemented in Europe. This study aimed to evaluate their impact in Denmark, Scotland, England and the Netherlands.

**Method:** Quarterly time series analyses measuring hydroxyzine initiation, discontinuation, and switching to other antihistamines, benzodiazepines and antidepressants in Denmark, England, Scotland and the Netherlands from 2009 to 2018. Data were analysed using interrupted time series regression.

**Results:** Hydroxyzine initiation in quarter one 2010 in Denmark, Scotland, England and the Netherlands per 100 000 was: 23.5, 91.5, 35.9 and 34.4 respectively. Regulatory action was associated with a significant: immediate fall in hydroxyzine initiation per 100 000 in England (−12.05, 95%CI −18.47 to −5.63) and Scotland (−19.01, 95%CI −26.99 to −11.02); change to a negative trend in hydroxyzine initiation per 100 000/quarter in England (−1.72, 95%CI −2.69 to −0.75) and Scotland (−2.38, 95%CI −3.32 to −1.44). Regulatory action was associated with a significant: immediate rise in hydroxyzine discontinuation per 100 000 in England (3850, 95% CI 440-7240). No consistent changes were observed in the Netherlands or Denmark. Regulatory action was associated with no switching to other antihistamines, benzodiazepines or antidepressants following hydroxyzine discontinuation in any country.

**Conclusion:** The 2015 EMA regulatory action was associated with heterogeneous impact with reductions in hydroxyzine initiation varying by country. There was limited

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impact on discontinuation with no strong evidence suggesting unintended consequences of major switching to other antihistamines, benzodiazepines or antidepressants.

**KEYWORDS**

hydroxyzine, pharmacoepidemiology, pharmacovigilance, prescribing, regulation, time-series

## 1 | INTRODUCTION

Hydroxyzine is an antihistamine approved in Europe for the management of anxiety, skin and sleep disorders. In February 2015, the European Medicines Agency (EMA) examined the proarrhythmogenic potential of hydroxyzine based on evidence from clinical and post-marketing safety data.<sup>1</sup> The EMA safety review concluded that although hydroxyzine containing medicinal products are effective treatments for their approved indications, in order for the benefit–risk balance of hydroxyzine to remain favourable, contraindications, warnings, and changes to the product information, including a direct healthcare professional communication (DHPC) were required to be implemented across the European Union (EU). Hydroxyzine was contraindicated in people with cardiovascular disease (CVD) and in those prescribed medicines known to prolong the QT interval.<sup>1</sup>

When new safety information emerges about a medicine, effective communication is essential to minimise harm. The benefit–risk profile of medicines is constantly evaluated by the EMA, which is responsible for cascading new safety information through the European pharmacovigilance network to alert prescribers and patients. However, the impact of such regulatory actions on healthcare professional behaviour is often poorly understood despite their enormous potential to affect public health.<sup>2,3</sup> One of the EMAs responsibilities now includes measuring the effectiveness of their regulatory actions, which led the EMA to commission a study on hydroxyzine to support the EMA Pharmacovigilance Risk Assessment Committee (PRAC) decision making. The aim of this study was therefore to evaluate the impact of the EMA risk minimisation measures implemented in 2015 following the EMA PRAC referral procedure for hydroxyzine using data from Denmark, England, Scotland, and the Netherlands.

## 2 | METHODS

### 2.1 | Data sources

Four data sources were analysed (please see Supporting Information Methods for further details). In brief these were:

- The Clinical Practice Research Datalink (CPRD), which contains primary care data. For this analysis only up-to-standard data from English practices within the UK was used.<sup>4</sup>

### KEY POINTS

- Hydroxyzine initiation fell following the 2015 EMA regulatory action
  - EMA regulatory action had a variable effect on hydroxyzine initiation
  - EMA regulatory action was associated with no major switching to other antihistamines, benzodiazepines or antidepressants
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- The Scottish Prescribing Information System (PIS), which records all dispensed medicines from pharmacies in Scotland (UK) that can be record-linked to demographic data, hospital admissions and attendances, and death registrations nationally within Scotland.<sup>5</sup>
  - The Danish Register of Medicinal Products, which records all out-of-hospital prescriptions and allows linkage of drug exposures to inpatient and outpatient hospital contacts in the Danish National Patient Registry, including death data from the Civil Registration System.<sup>6–8</sup>
  - The Dutch PHARMO Database Network, which combines data from primary and secondary care in the Netherlands. These different data sources, including data from general practices, in- and out-patient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, and which are linked on a patient level through validated algorithms.<sup>9</sup>

### 2.2 | Study population

Cohorts were generated to provide time series data for analysis using a common protocol (EU PAS Register number EUPAS24089).<sup>10</sup> The start period varied by the availability of data from each database. Cohort entry was defined as the latest of the following: study start date; date of registration with the general practice (in CPRD and PHARMO); availability of data collection; having at least 1 year of observation (lookback period). For cohorts associated with the target condition (a new contraindication), cohort entry was additionally defined by the date when the condition was first recorded. Contraindicated patients included those patients with: (a) a known risk factor to QT interval prolongation consisting of CVD disease and;

(b) concomitant use of medicines known to prolong the QT interval and/or induce Torsades de Pointes (please see Supporting Information Methods for further details).

A patient's index date was the latest of the study period start date, the date of birth, or their first database follow up date plus 1 year (to allow sufficient time to determine prevalent versus incident use of medicines). A patient's last follow up date was the first occurrence of the following: death (all databases); end of study period (varies between countries); end of registration within the data source (end of registration would not significantly affect data from Denmark and Scotland because they use national data that captures patients moving within the health system). A patient was included in the time period aggregate if the first and last day both lay between the patient's index date and their last follow up date, so patients were observable for the entire quarter.

### 2.3 | Exposure

The exposure was the conclusion of the 2015 EMA PRAC referral procedure when recommendations aimed at reducing the risk of heart rhythm disturbances associated with use of hydroxyzine first became public (Box 1).<sup>1</sup>

### 2.4 | Outcomes

The outcomes of interest evaluated whether there was any immediate change in prescribing at the time of the regulatory action (pre-specified as February 2015) and/or change in prescribing trend post-intervention compared to the baseline trend. These were analysed as a series of proportions from aggregated patient counts evaluated in each quarter over the study period.

#### Box 1 Summary of EMA recommended measures to minimise the risk of heart rhythm problems with hydroxyzine use

- Use must be avoided in patients who already have risk factors for heart rhythm disturbances or are taking other medicines that increase the risk of QT prolongation.
- Use is not recommended in the elderly.
- Use hydroxyzine at the lowest effective dose for as short a time as possible.
- The maximum daily dose of hydroxyzine should be no more than 100 mg in adults (50 mg in the elderly if use cannot be avoided), and 2 mg per kg body weight where used in children up to 40 kg in weight.
- Care is needed in patients taking medicines that slow the heart rate or decrease the level of potassium in the blood, as these also increase the risk of problems with heart rhythm.

- Hydroxyzine prescribing initiation overall
- Hydroxyzine prescribing initiation by recorded history of an indication, age, gender, and exposure type
- Hydroxyzine prescribing discontinuation overall
- Switching patterns to alternative medicines following hydroxyzine discontinuation

Hydroxyzine initiation was defined as a prescription for hydroxyzine with no exposure to hydroxyzine in the preceding 92 days. The denominator was the number of non-users on the first day of the time period defined as no exposure to hydroxyzine in the previous 92 days. Exposure type was defined as one-off use, sporadic use or chronic use. One-off users were defined as patients prescribed a single hydroxyzine prescription only. To define sporadic and chronic users we calculated a possession ratio for each patient defined by using the number of days prescribed (or supplied) assuming a standard daily dose divided by the number of days between hydroxyzine prescriptions. We defined sporadic users as patients with a hydroxyzine possession ratio of less than 1 standard day of therapy per 3 days. Patients with a hydroxyzine possession ratio of more than 1 standard day of therapy per 3 days were defined as chronic users. Hydroxyzine discontinuation was defined as the number of patients with a prescription for hydroxyzine with no further exposure to hydroxyzine in the 92 days following the date of prescription. The denominator was the number of patients prescribed hydroxyzine in the time period. The numerator was the number of patients discontinuing. For patients with contraindications to hydroxyzine, only hydroxyzine initiation was examined. A switch to an alternative medicine class was defined as those patients who discontinued hydroxyzine and who then initiated a drug in the class listed in Table S6. Initiation of an alternative medicine was defined as the first prescription of a drug in that class prescribed within 92 days following the date of the last hydroxyzine prescription. Please see online Supporting information methods section for further details.

### 2.5 | Statistical analysis

The study design was an interrupted time series regression analysis of prescribing trends. The primary analysis used interrupted time series regression to fit quarterly time trends for each country. The effect of the intervention for each country was represented either by a step function, or by a continuous linear function modelling the baseline slope before the intervention time point, the change in slope from the baseline time periods to the post-intervention time periods and the immediate change associated with the intervention time point as described by Wagner et al.<sup>11</sup> Interrupted time series regression was done for hydroxyzine initiation rates, hydroxyzine discontinuation rates, and for patients switching to the alternative classes of medicines stratified by country. Time points with cell counts fewer than five were suppressed. Before fitting all regression models, the data was visualised graphically. Trends were modelled using weighted linear regression, the weights being the denominators in each proportion. All models were checked for autocorrelation using the Durbin-

Watson statistic. All analyses were carried out using SAS Version 9.4 Copyright 2002–2012 SAS Institute Inc., Cary, North Carolina.

### 3 | RESULTS

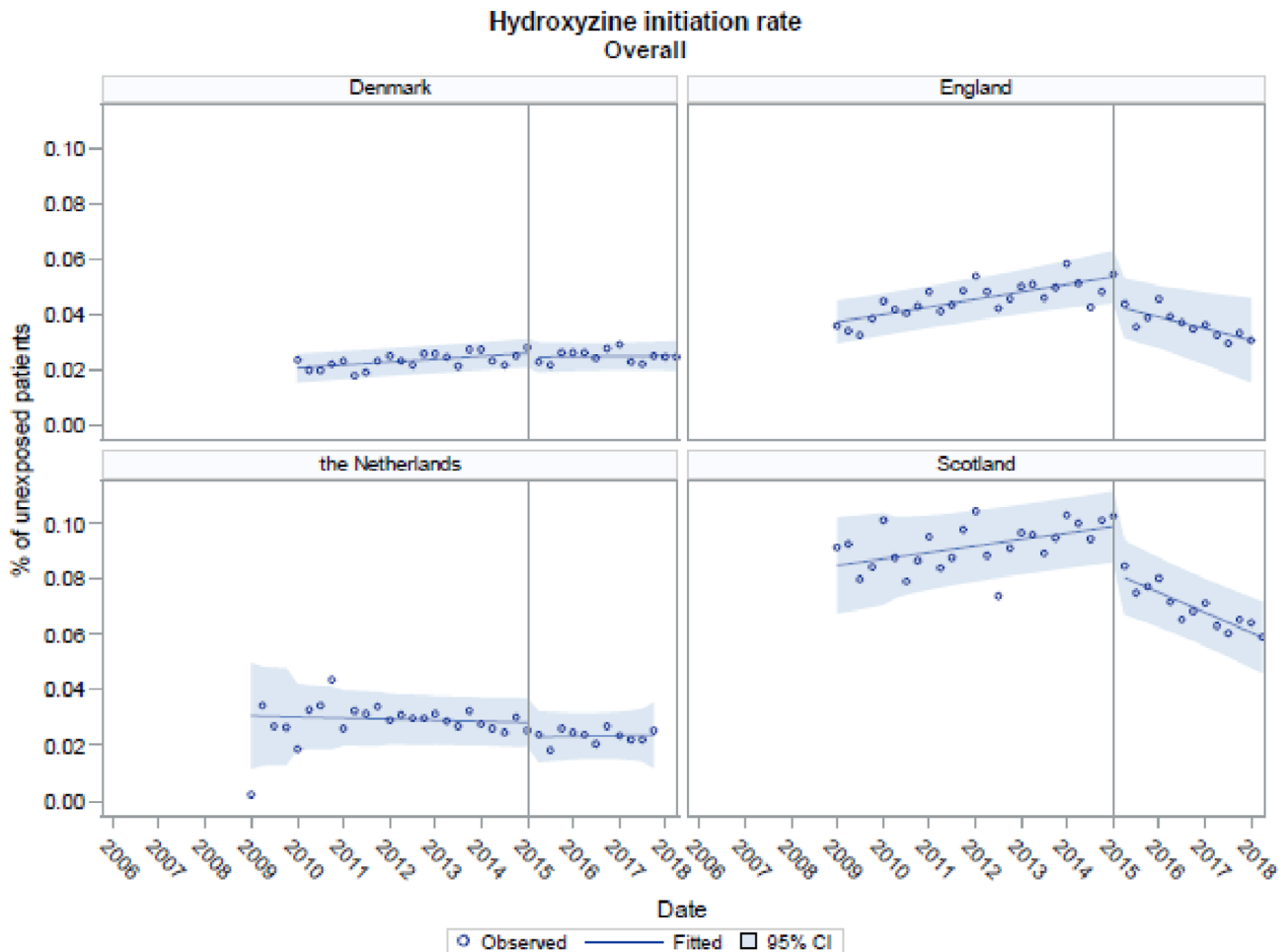
#### 2.6 | Ethical permissions

Permission to conduct the study in each database was obtained from the relevant source from each country, according to each databases' standard terms and conditions.

Over the study period the population consisted of approximately: 5.6 million from Denmark; 5.3 million from Scotland; 4.2 million from England; and 1 million from the Netherlands. The prevalence of hydroxyzine initiation at baseline per 100 000 patients was 23.5 in Denmark, 91.5 in Scotland, 35.9 in England and 34.4 in the Netherlands (Table 1). Over the study period the prevalence of hydroxyzine initiation fell, apart from in Denmark. The most common recorded

**TABLE 1** Prevalence of hydroxyzine initiation at the beginning and end of overlapping follow-up periods for each country

Country	Baseline		Final		Changes in hydroxyzine initiation (95%CI)	
	Quarter	Prevalence of hydroxyzine initiation (per 100 000)	Quarter	Prevalence of hydroxyzine initiation (per 100 000)	Absolute (per 100 000)	Relative (%)
Denmark	2010Q1	23.5	2018Q1	24.6	1.1 (–1.4 to 3.3)	4.7 (–6.0 to 14.0)
England	2009Q1	35.9	2018Q1	30.8	–5.1 (–10.3 to 0.3)	–14.2 (–28.7 to 0.8)
The Netherlands	2009Q2	34.4	2017Q4	25.4	–9 (–20.7 to 1.9)	–26.2 (–60.2 to 5.5)
Scotland	2009Q1	91.5	2018Q2	58.9	–32.6 (–38.2 to –27.1)	–35.6 (–41.7 to –29.6)

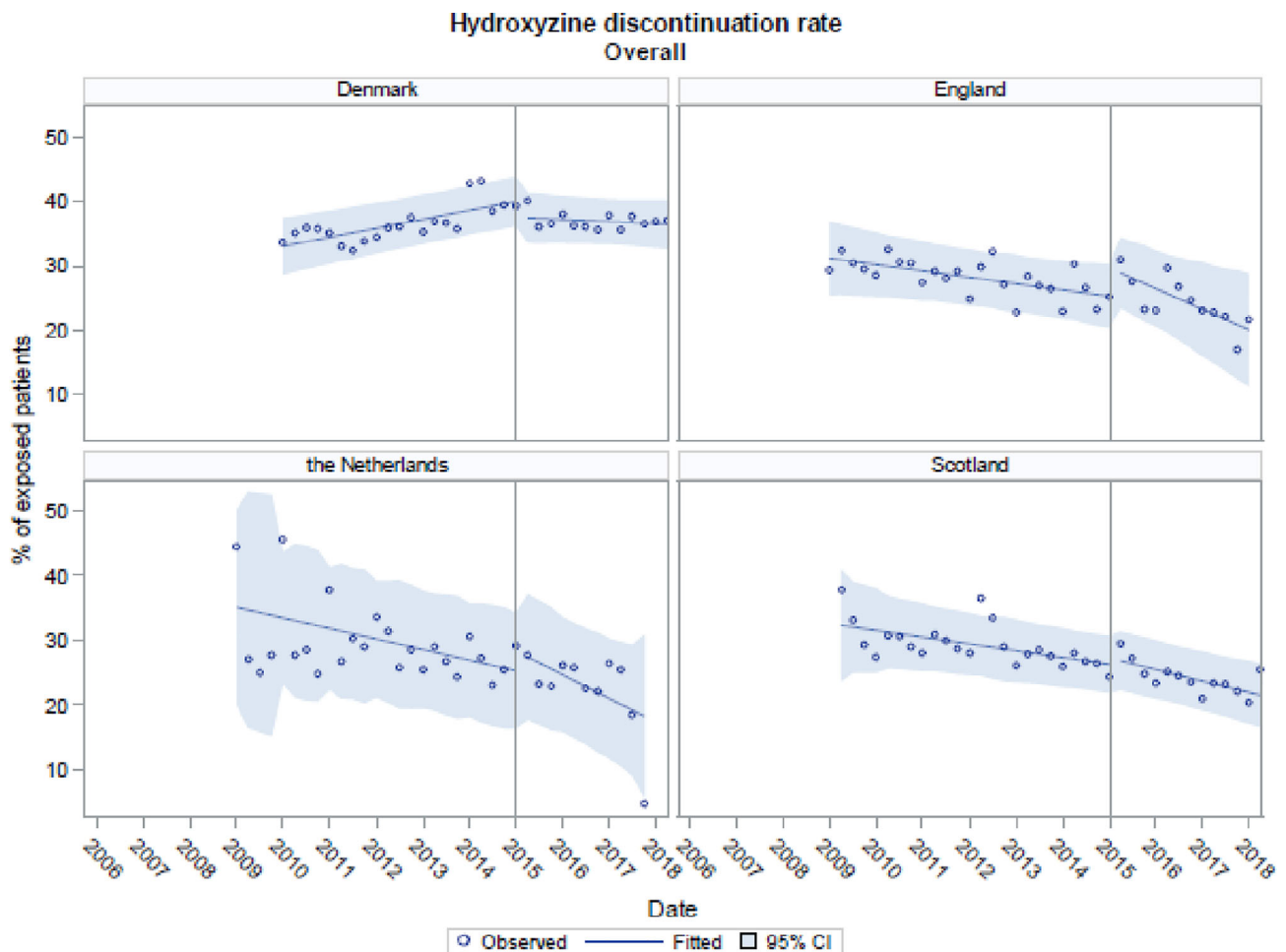


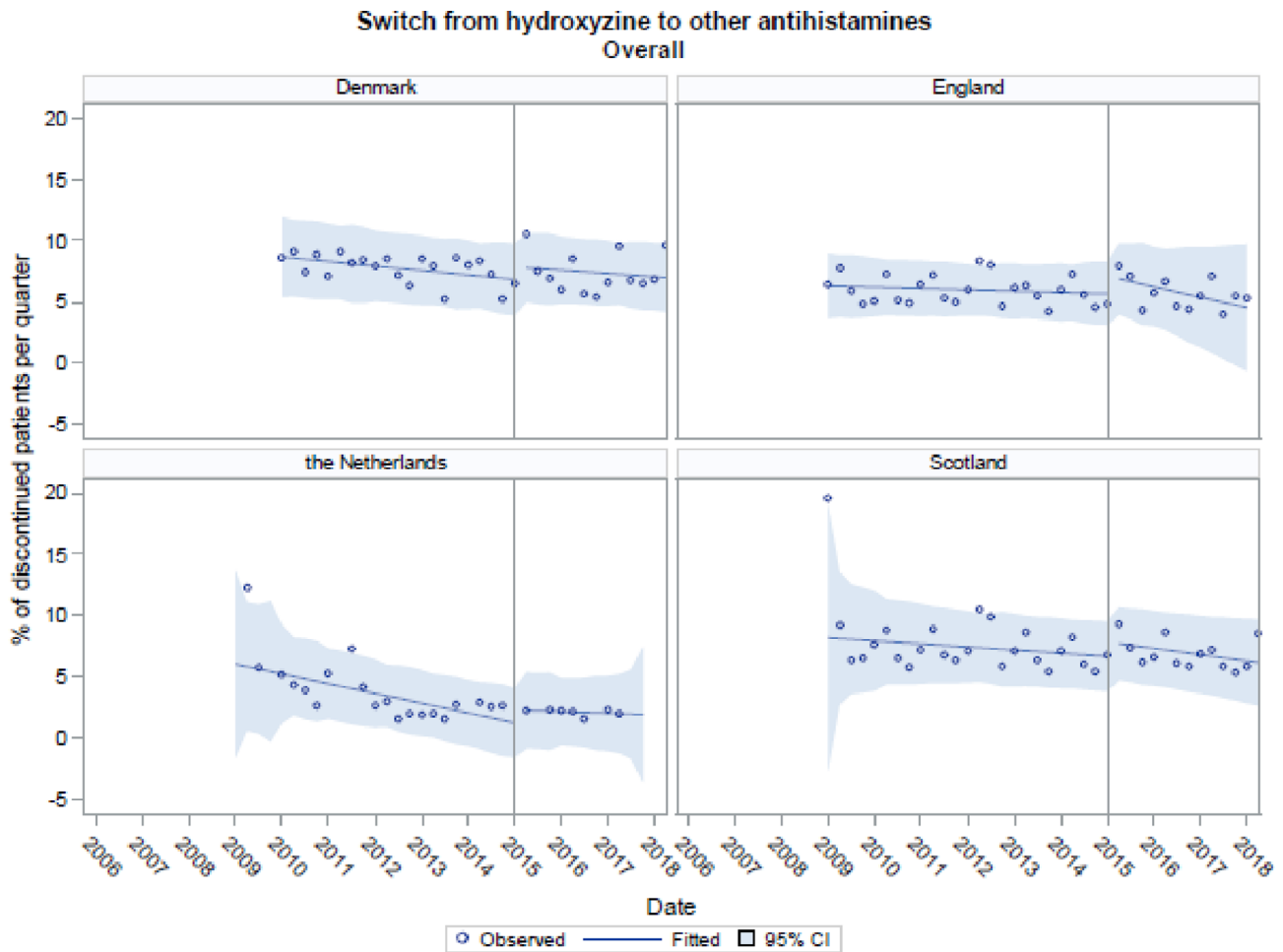
**FIGURE 1** Trends in overall hydroxyzine initiation in Denmark, England, the Netherlands and Scotland [Colour figure can be viewed at wileyonlinelibrary.com]

**TABLE 2** Interrupted time series regression results for trends in hydroxyzine initiation and discontinuation in each country

Country	Trend (95% CI) in hydroxyzine initiation before February 2015 (per 100 000/quarter)	Change (95% CI) in hydroxyzine initiation in first quarter after February 2015 (per 100 000)	Change in trend (95% CI) in hydroxyzine initiation after February 2015 (per 100 000/quarter)
<i>Initiation</i>			
Denmark	0.27 (0.10 to 0.44)	-1.66 (-4.93 to 1.61)	-0.22 (-0.61 to 0.16)
England	0.68 (0.46 to 0.89)	-12.05 (-18.47 to -5.63)	-1.72 (-2.69 to -0.75)
The Netherlands	-0.10 (-0.40 to 0.20)	-5.08 (-10.92 to 0.77)	0.16 (-0.70 to 1.03)
Scotland	0.58 (0.21 to 0.96)	-19.01 (-26.99 to -11.02)	-2.38 (-3.32 to -1.44)
<i>Discontinuation</i>			
Denmark	346 (211 to 481)	-2905 (-5328 to -481)	-425 (-710 to -139)
England	-246 (-375 to -116)	3852 (439 to 7264)	-558 (-109 to -23)
The Netherlands	-409 (-710 to -108)	2560 (-3660 to 8781)	-512 (-1435 to 412)
Scotland	-263 (-414 to -112)	794 (-2082 to 3671)	-181 (-529 to 167)

Note: The denominator for hydroxyzine initiation was the number of non-users on the first day of the time period defined as no exposure to hydroxyzine in the previous 92 days. The denominator for hydroxyzine discontinuation was the number of patients prescribed hydroxyzine in the time period.

**FIGURE 2** Trends in overall hydroxyzine discontinuation in Denmark, England, the Netherlands and Scotland [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**FIGURE 3** Trends in switching from hydroxyzine to other antihistamines in Denmark, England, the Netherlands and Scotland [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

history of an indication in people initiating hydroxyzine in all countries was skin disorder.

### 3.1 | Impact of the regulatory action on hydroxyzine initiation

Trends in overall hydroxyzine initiation in each country are shown in Figure 1 and in Table 2. In Denmark, England and Scotland there was a positive trend in hydroxyzine initiation at baseline, whilst in the Netherlands there was no trend. In England and Scotland the regulatory action was associated with an immediate fall in hydroxyzine initiation ( $-12.05$ , 95%CI  $-18.47$  to  $-5.63$  per 100 000 and  $-19.01$ , 95%CI  $-26.99$  to  $-11.02$  per 100 000 respectively). No immediate change was observed in Denmark or the Netherlands (Table 2). Post-intervention, the regulatory action was associated with a change to a negative trend in hydroxyzine initiation in England and Scotland ( $-1.72$ , 95%CI  $-2.69$  to  $-0.75$  per 100 000/quarter and  $-2.38$ , 95%CI  $-3.32$  to  $-1.44$  per 100 000/quarter

respectively). No change in trend was observed in Denmark or the Netherlands.

### 3.2 | Trends in hydroxyzine initiation stratified by age, gender and exposure type

Trends in hydroxyzine initiation by age, gender and exposure type are shown in Figures S1 to S4 and Tables S1 to S4. Hydroxyzine initiation was greater in women than men and consisted mainly of one-off use. The regulatory intervention was associated with immediate reductions: in all exposure types in England; one-off and sporadic exposure in Scotland; sporadic exposure in the Netherlands. Post-intervention, there was a change to a negative trend in all exposure types in England and one-off and chronic exposure in Scotland.

Hydroxyzine initiation increased with age. In general, trends for hydroxyzine initiation by age in England and Scotland followed overall trends (Tables S2 and S3). In Denmark, a negative trend in hydroxyzine initiation was observed in people aged 18–29 and 30–39 years

**TABLE 3** Interrupted time series regression results for trends in switching to alternative medicines

Country	Trend (95% CI) in switching to alternative medicines before February 2015 (per 100 000/quarter)	Change (95% CI) in switching to alternative medicines in first quarter after February 2015 (per 100 000)	Change in trend (95% CI) in switching to alternative medicines after February 2015 (per 100 000/quarter)
<i>Denmark</i>			
Other antihistamines	-92 (-193 to 9)	1058 (-706 to 2823)	24 (-161 to 208)
Benzodiazepines	-76 (-144 to -9)	263 (-906 to 1431)	-13 (-135 to 110)
Other medications	66 (-9 to 141)	-471 (-1775 to 832)	-101 (-237 to 36)
<i>England</i>			
Other antihistamines	-27 (-92 to 38)	1237 (-587 to 3061)	-187 (-486 to 112)
Benzodiazepines	7 (-14 to 27)	184 (-423 to 791)	-50 (-175 to 76)
Other medications	1 (-34 to 36)	172 (-818 to 1162)	-17 (-179 to 145)
<i>The Netherlands</i>			
Other antihistamines	-200 (-308 to -92)	1216 (-1084 to 3516)	165 (-232 to 562)
Benzodiazepines	-73 (-112 to -33)	481 (-493 to 1456)	31 (-1232 to 1293)
Other medications	122 (-1539 to 1783)	372 (-2350 to 2424)	-355 (-3503 to 2792)
<i>Scotland</i>			
Other antihistamines	-63 (-158 to 31)	1092 (-790 to 2975)	-65 (-300 to 171)
Benzodiazepines	-24 (-40 to -8)	315 (-6 to 635)	31 (-10 to 71)
Other medications	-27 (-67 to 14)	-99 (-909 to 711)	95 (-6 to 196)

Note: The denominator for switching was the number of patients discontinuing hydroxyzine in the time period. Other medications = tricyclic antidepressants, mirtazapine and SSRIs.

**TABLE 4** Interrupted time series regression results for trends in hydroxyzine initiation in patients with contraindications to hydroxyzine in each country

Contraindication per country	Trend (95% CI) in hydroxyzine initiation before February 2015 (per 100 000/quarter)	Change (95% CI) in hydroxyzine initiation in first quarter after February 2015 (per 100 000)	Change in hydroxyzine initiation in trend (95% CI) after February 2015 (per 100 000/quarter)
<i>Cardiovascular disease</i>			
Denmark	0.13 (-0.46 to 0.72)	-7.22 (-18.11 to 3.67)	-0.02 (-1.31 to 1.26)
England	2.06 (1.30 to 2.82)	-36.47 (-59.42 to -13.51)	-3.20 (-6.75 to 0.36)
The Netherlands	-1.48 (-2.61 to -0.35)	-5.73 (-22.81 to 11.35)	1.14 (-1.26 to 3.55)
Scotland	1.27 (0.25 to 2.29)	-46.16 (-69.98 to -22.34)	-3.79 (-6.60 to -0.98)
<i>QT prolonging medicines<sup>a</sup></i>			
Denmark	1.74 (1.02 to 2.45)	-7.03 (-20.97 to 6.92)	-1.69 (-3.36 to -0.022)
England	2.26 (1.45 to 3.07)	-57.06 (-84.69 to -29.44)	-8.51 (-16.24 to -0.77)
The Netherlands	-1.68 (-2.86 to -0.50)	-7.89 (-31.14 to 15.37)	2.05 (-1.36 to 5.45)
Scotland	1.90 (0.95 to 2.85)	-50.10 (-71.07 to -29.12)	-7.45 (-9.92, -4.98)

<sup>a</sup>And/or medicines known to induce Torsades de Pointe. The denominator for hydroxyzine initiation was the number of non-users on the first day of the time period defined as no exposure to hydroxyzine in the previous 92 days for each target cohort.

with an immediate fall in those aged 60–69 years (Table S3). In the Netherlands an immediate fall was observed in people aged 18–29 and 60–69 years (Table S4).

### 3.3 | Impact of the regulatory action on hydroxyzine discontinuation

The results for hydroxyzine discontinuation are shown in Figure 2 and in Table 2. The baseline trend in hydroxyzine discontinuation

was negative in all countries apart from in Denmark, where there was a positive trend. In Denmark, the regulatory action was associated with an immediate fall in hydroxyzine discontinuation (-2905, 95%CI -5328 to -481 per 100 000) and a change to a negative trend (-425, 95%CI -710 to -139 per quarter) post-intervention. In England, the regulatory action was associated with an immediate rise in hydroxyzine discontinuation (3852, 95%CI 439-7264) and a change to a negative trend in discontinuation (-558, 95%CI -109 to -23). No changes were observed for Scotland and the Netherlands.



### 3.4 | Impact of the regulatory action on switching to other antihistamines, benzodiazepines or antidepressants

Trends in switching to alternative medicines are shown in Figure 3, Figures S5 and S6 and in Table 3. The regulatory action was associated with no immediate change in switching to other antihistamines, benzodiazepines or antidepressant and no significant change in trend post-intervention in any country.

### 3.5 | Impact of the regulatory action on hydroxyzine initiation in patients with contraindications

Trends in hydroxyzine initiation by contraindication are shown in Table 4 and Figures S7 and S8. The baseline trend in hydroxyzine initiation in patients with CVD was positive in England and Scotland, negative in the Netherlands. The regulatory action was associated with an immediate fall in hydroxyzine initiation in patients with CVD in Scotland and England and a change to a negative trend in Scotland post-intervention.

The baseline trend in hydroxyzine initiation in patients prescribed medicines known to prolong the QT interval and/or induce Torsades de Pointes was positive in all countries apart from the Netherlands, which had a negative trend. The regulatory action was associated with an immediate fall in hydroxyzine initiation in these patients in Scotland and England and a change to a negative trend in Scotland, England and Denmark post-intervention.

## 4 | DISCUSSION

Over the study period, the prevalence of hydroxyzine initiation fell by 36, 26 and 14% in Scotland, England and the Netherlands respectively but not in Denmark. The EMA regulatory action for hydroxyzine was associated with immediate falls in hydroxyzine initiation in England and Scotland by 12 and 19 per 100 000 respectively, which represented a ~20% immediate fall compared to the preceding quarter. In Denmark and the Netherlands impact was more limited, with evidence suggesting it may have occurred only in certain age groups, and for Denmark, in those prescribed medicines known to affect the QT interval. The regulatory action was associated with an immediate 15% rise in hydroxyzine discontinuation in England compared to the previous quarter. However, no impact on hydroxyzine discontinuation was observed in the Netherlands or Scotland, whilst a fall was observed in Denmark. The regulatory action was not associated with a major impact on switching to other antihistamines, benzodiazepines or antidepressants.

The use of hydroxyzine in each country was low suggesting it was not the clinically preferred antihistamine. For example, although Scotland had the highest prevalence of hydroxyzine initiation, being approximately fourfold higher compared to the Netherlands and

Denmark, in 2016 it represented only 4.9% of all antihistamine prescribing in Scotland.<sup>12</sup>

For regulatory actions to be effective, knowledge should be effectively disseminated, communicated and understood, and how this occurs may affect the size of any impact.<sup>13</sup> If prescribing levels are already very low, it is possible that regulatory actions may struggle to demonstrate significant impact unless particularly focused on a narrow target population. This is because healthcare professionals may perceive them as being less important and may not be widely discussed among educational resources or incorporated into guidelines. In this regard, it is possible that use may already be limited to those patients who have a real need for the medicine (i.e., that it has established effectiveness so that they are less likely to discontinue treatment). Despite levels of prescribing being low in all countries, variation in impact was still observed. Therefore perceived lack of importance or established effective use among people who need treatment are perhaps less likely explanations.

Heterogeneity in impact can be associated with the type of warning and method of dissemination. For example, DHPCs have been associated with an average change in targeted prescribing of 47% compared to 13% communicated via drug bulletins.<sup>14</sup> In this regard, a 2004 UK risk communication relating to antipsychotic use in dementia disseminated via DHPC led to greater changes in prescribing in Scotland compared to a 2009 less-specific communication detailed in a drug bulletin. Differences were observed between Scotland and England.<sup>15,16</sup> Furthermore, heterogeneity may result from differences in the timing of implementation within each country. For example the DHPCs appear to have been disseminated on 21 April, 27 April and 4 May in the Netherlands, UK and Denmark respectively.<sup>17-19</sup> However, other downstream factors may also have influenced this process and therefore we used the quarter when the referral concluded as our intervention time point when information first became public. Nevertheless, we add to the evidence demonstrating geographical variation in the impact of pharmacovigilance decisions can occur despite being subject to the same recommendations.<sup>3,20-25</sup>

Regulatory interventions may be associated with unintended consequences such as substitute prescribing or switching that may themselves lead to adverse effects.<sup>20,26</sup> Evaluating such effects, is often subject to methodological limitations.<sup>2,3</sup> Specific to hydroxyzine, it would be of concern if patients switched to benzodiazepines that are associated with an increased risk of addiction and mortality to manage anxiety.<sup>27</sup> Similarly, switching to an antihistamine with more sedative properties may also have unintended effects such as increasing road traffic accidents.<sup>28</sup> Reassuringly, we observed there is no strong evidence suggesting the regulatory action for hydroxyzine caused widespread substitute prescribing for those medicines that we evaluated.

We noted that the regulatory action seemed to have less impact on hydroxyzine discontinuation compared to initiation. This would be in keeping with the findings from a systematic review examining the impact of United States risk advisories, which suggested such advisories were more effective at decreasing initiation of targeted medicines and less effective at bringing about their discontinuation.<sup>2</sup> This has also been seen with another recent European study.<sup>20</sup> While



the immediate rise in hydroxyzine discontinuation in England is considered an intended effect, it is uncertain why hydroxyzine discontinuation should have fallen in Denmark particularly when the rate of hydroxyzine initiation did not change. However, the post-intervention negative trend in discontinuation in England may be because the pool of hydroxyzine initiators was falling, an effect seen elsewhere.<sup>20</sup>

#### 4.1 | Strengths and limitations

To our knowledge, this study is the largest study examining hydroxyzine prescribing in Europe, the findings of which may support the EMA strategy for examining the impact of pharmacovigilance decisions. It uses high quality data sources and a common protocol and data extraction method to standardise data from each country. However, the study has several potential limitations. Firstly, our data sources do not capture over the counter antihistamine use that may underestimate the prevalence of switching to other antihistamines. Furthermore, indications were determined by coded diagnoses that are more commonly recorded in primary care than hospital data sources. For this reason the proportion of patients with an indication was greater for England and the Netherlands compared to Denmark and Scotland, which report trends for patients with indications attending secondary care. Secondly, due to the lower prevalence of hydroxyzine exposure, many subgroup analyses meant that cell counts less than five were detected that affected precision and their ability to be reported. Thirdly, although ITS analysis is a robust quasi-experimental design commonly used to evaluate policy interventions, it only examines associations that may be confounded by other interventions occurring simultaneously.<sup>29</sup> Data presented in this manuscript are population-average estimates. Therefore variation may still exist among other groups that have not been studied such as general practices. Recommendations from this study may not be generalizable to areas within Europe that were not studied.

In conclusion, the EMA 2015 regulatory action targeting the safety of hydroxyzine products was associated with consistent reductions in hydroxyzine initiation in two of the four countries, whilst having limited impact on discontinuation and no switching of switching to the classes of medication that we examined.

#### ACKNOWLEDGEMENTS

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#### CONFLICT OF INTEREST

Elisabeth Smitsm Jetty A. Overbeek and Ron M. C. Herings are employees of the PHARMO Institute for Drug Outcomes Research.

This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. TMM's university holds research grants from Novartis, Ipsen, Teijin & Menarini. He is or has been the Principal Investigator on trials paid for by Novartis, Ipsen, Teijin, RTI, GlaxoSmithKline, SHIRE and Menarini. In the last 3 years he has been paid consulting fees by Novartis and Merck. None of these studies relate to hydroxyzine.

#### AUTHOR CONTRIBUTIONS

All authors were involved in the study design, approval of the study protocol, interpretation of results and drafting of the manuscript.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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