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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

# Reported time to onset of neurological adverse drug reactions among different age and gender groups using metoclopramide: an analysis of the global database Vigibase®.

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## Abstract

**Purpose** Despite FDA and EMA warnings of long-term use, little is known regarding the time to onset (TTO) of neurological adverse drug reactions (ADR) for metoclopramide. The aims of this study were, first, to evaluate whether neurological ADRs are more commonly reported for metoclopramide than for other medications, and second, to describe how time to onset of neurological ADRs differs by age and gender.

**Methods** All ADR reports with metoclopramide as the suspected/interacting drug were extracted from the WHOs Global ADR database Vigibase® between 1967 and May 2016. Cox proportional hazards models were fit using TTO of neurological ADRs as the outcome and age, gender, and type of ADR as predictors. Proportional Reporting Ratios (PRRs) for neurological ADRs were compared across age and gender. Lawyer reports were excluded in the analysis.

**Results** Over 47,000 ADR reports with metoclopramide were identified. Over one third (35.6%) of the reports came from lawyers. The majority of ADRs in general and neurological ADRs in specific occurred within the first 5 days of metoclopramide use (median 1 day). TTO increased with age. Neurological ADRs were reported two to four times as frequently for metoclopramide than for other drugs, with the highest PRRs observed in children (PRR = 4.24 for girls and 4.60 for boys).

**Conclusions** Most adverse drug reactions occur within the first 5 days of treatment with metoclopramide. Patients requiring use of metoclopramide should be carefully monitored for neurological ADRs during the first days of treatment.

**Keywords** Metoclopramide · Vigibase · Adverse drug reactions

**Key findings:** • For patients aged 45 and older, the reported time to onset for ADRs was longer than for younger patients, particularly for reports of tardive dyskinesia.
• Almost all ADRs occurred within the first 5 days of metoclopramide treatment initiation.
• A higher proportion of reported ADRs were neurological for metoclopramide compared to other medicines, regardless of age and gender.
• More than one third of all ADR reports were communicated by US lawyers after FDA warnings in 2009.

Preliminary results from this study were presented in a poster and Pecha Kucha presentation at the European Society of Clinical Pharmacy (ESCP) symposium, Oslo, October 2016 and in a Pecha Kucha presentation at the Norwegian Pharmacists Associations annual conference, Oslo, November 2016.

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## Introduction

Metoclopramide is a dopamine-receptor ($D_2$) antagonist used for its prokinetic and antiemetic properties. Authorized indications include nausea and vomiting and gastrointestinal motility disorders [1, 2]. The use of metoclopramide has, as with other dopamine-receptor antagonists, been associated with an increased risk of neurological side effects and drug-induced movement disorders such as tardive dyskinesia (TD) [3–7].

In 2009, following study findings showing that 20% of patients took metoclopramide for more than the recommended 3 months and that a majority of spontaneous adverse event reports occurred in patients taking metoclopramide for longer than the recommended 12 weeks [8], the US Food and Drug Administration (FDA) issued a black box warning for metoclopramide aimed to reduce use of the drug for periods longer than 12 weeks [9]. In 2013, following requests from the French Market Authorisation Committee related to a nationwide French study of the risk-benefit balance of metoclopramide, the European Medicines Agency recommended that metoclopramide be used only for short-term use (maximum 5 days) and that the maximum dose should restricted to 30 mg per day [1].

Both the FDA and European Medicines Agency (EMA) warnings were aimed at minimizing the risk of serious neurological adverse drug reactions. However, the FDA and EMA warnings did not vary by age or gender, nor did they consider use among pregnant or breastfeeding women. Metoclopramide is commonly used to treat nausea and vomiting during pregnancy [10], as well as during lactation to increase milk production [11]; both of these indications generally exceed the EMA recommendation for maximum treatment duration, and may exceed FDA's recommendation as well. Metoclopramide is widely considered to be a safe treatment during pregnancy as it is not associated with poor pregnancy or child outcomes, such as major congenital malformations, low birth weight, or prenatal death [12, 13]. Because the FDA and EMA recommendations apply to all ages and genders, some women may forgo needed treatment during pregnancy and lactation.

Little is known regarding the time to onset (TTO) of neurological ADRs among women of reproductive age, as well as for other age and gender groups. A better understanding of risks specific to age and gender groups could allow more appropriate treatment for pregnant and lactating women. Therefore, the two main aims of this study were, first, to evaluate whether neurological ADRs are more commonly reported for metoclopramide than for other medications, and second, to describe how time to onset of neurological ADRs and TD differs between age and gender groups. Additionally, we examined reporting frequency for metoclopramide before and after the EMA and FDA warnings were issued.

## Method and material

### Data source

This study used spontaneously reported ADRs from the World Health Organization's (WHO) global Individual Case Safety Report (ICSR) database Vigibase®. Vigibase® is maintained by the Uppsala Monitoring Centre (UMC), WHO's Collaborating Centre for International Drug Monitoring. The UMC receives reports of suspected adverse reactions to medical products from the 125 countries participating in the WHO Programme for International Drug Monitoring, and stores the information in Vigibase®. The information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases [14].

Each ICSR of a suspected ADR (referred to as "ADR report(s)") contains anonymous administrative data (e.g., reporting country, notifier, such as a physician, consumer, or lawyer), patient information (e.g., gender, age), information about medicine use (e.g., start day, stop day, dosage, co-medication), and the ADR (e.g., reaction date, type of reaction). All ADR reports with metoclopramide as the suspected or interacting drug registered between 1967 and May 2016 were extracted from the database. Two levels of the WHOART terminology were used in the analysis: Preferred Term (PT), which provides a precise identification of a reaction, and System Organ Class (SOC), which provides a broad definition based on system affected [15]. Figure 1 provides a detailed flow chart for inclusion and exclusion in the analyses used in this study.

### Variables used

TTO was calculated as the time from the reported start date of metoclopramide to the first date of onset of an ADR in the report. Hence, it represents the time from when treatment with metoclopramide was initiated to when the ADR occurred. In reports where the patient had used metoclopramide with multiple start dates, the first start date was used.

Patients were categorized into age and gender groups as shown in Table 1. "Women of reproductive age" refers to the category of women aged 18–44 years.

Reporting year and reporting region were used as covariates. The year the report was received was grouped as follows: 1968–1988, 1989–July 2009, August 2009–2012, 2013–1st of May 2016. The groups were chosen to capture the influence warnings issued in July 2009 and January 2013. Reporting country was coded into one of the following regions: France, the Nordic countries (Sweden, Norway, Denmark, Finland, and Iceland), the rest of Europe, the USA, and the rest of the world. France and the USA were grouped separately from the other countries due to a possible increased focus on

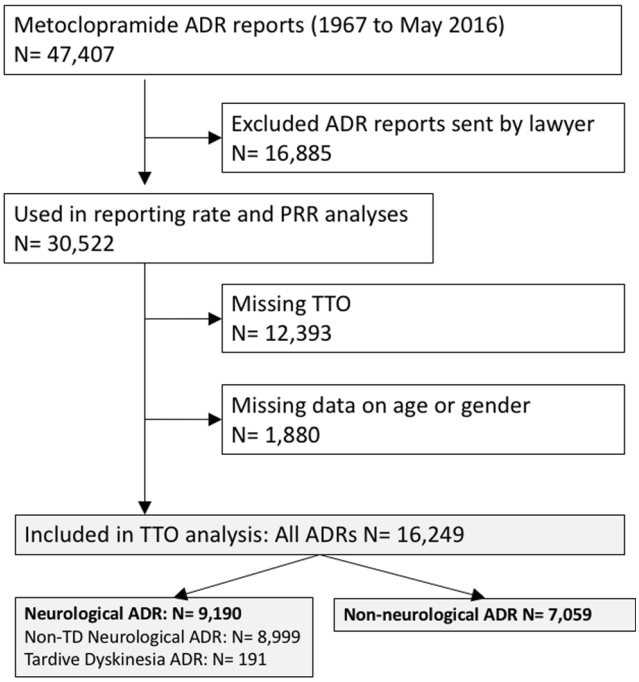


**Fig. 1** Overview of inclusion and exclusion of adverse drug reaction reports included in the study

the risk-benefit balance of metoclopramide and hence, increased media attention [1, 16].

## Statistical analysis

All reports with metoclopramide as the suspected or interacting drug were included in the descriptive analyses. The patient characteristics, report characteristics, and ADR characteristics were stratified into all reports and reports not sent in by lawyers. All reports were used for the calculated Proportional Reporting Ratio (PRR) values. Reports sent in by lawyers were *excluded from multivariable-adjusted time to onset analyses*, as shown in Fig. 1.

To evaluate whether neurological ADRs are more commonly reported for metoclopramide than for other medications, we used the PRR and its 95% confidence intervals (CI) as provided by the UMC. A calculated PRR greater than 1 suggests that the adverse event is more commonly reported for individuals taking metoclopramide, relative to all other medicines [17]. The method is used by EMA to detect disproportionate reporting of drug-event pairs. The algorithm is found to perform similarly to other methods of signal detections available [18]. PRR values for metoclopramide were calculated for neurological ADRs as defined by the SOC term "neurological disorders," and for tardive dyskinesia specifically.

To examine how time to onset of neurological ADRs and TD differs between age and gender groups, we conducted univariate and multiple Cox regression analyses with TTO of ADR as outcome variable, with analyses stratified by (1) type of ADR and (2) neurological ADR reports with and without TD. Models were adjusted for region and the time period reports was received. A substantial fraction of the sample was missing information on age and gender (17%), and/or time to onset (41%). A total of 53% of reports were missing either age/gender or time to onset. We have elected to present complete case analyses for models using these variables. In these analyses, a hazard ratio (HR) < 1 suggests that events accumulate more slowly in the specified group, while an HR > 1 suggests that events occur more quickly. Cumulative hazard Kaplan-Meier curves of different TTO profiles according to age and gender are also presented.

We also studied the reporting frequency for ADRs before and after the FDA (July 2009) and EMA (December 2013) warnings were issued, and created bar graphs describing the percentage of reports received annually by Vigibase® from each geographic region. For this analysis, France, the Nordic countries, and all other European countries were combined into a single category, and reports from lawyers were excluded.

All statistical analyses were performed in Stata (version 14.2).

## Results

This study includes 47,407 ADR reports in which metoclopramide was a suspected or interacting medicine, as registered in Vigibase®. Characteristics of these reports are presented in Table 1. A total of 16,885 (35.6%) of the reports were sent in by a lawyer, of which 16,824 (99.6%) came from the USA between January 1 2009–May 1 2016. In total, 89.9% of the reports sent in by lawyers included tardive dyskinesia as an ADR. We excluded reports from lawyers in all analyses.

The most commonly reported ADRs on the SOC level of coding were neurological ADRs, occurring in 71.7% of the reports. The most common ADR on the preferred term level of coding was extrapyramidal disorders, occurring in 37.2% of the reports (Table 1). The second most common ADR was TD, which was reported in 34.8% of all reports. However, after removing reports sent in by lawyers, only 4.4% of the reports were for TD. Most metoclopramide-related reports (72.1%) were received between 2009 and 2016, as shown in Table 1.

About 55% of patients in the non-lawyer reports were women, and the mean age for these reports was 38 years (SD: 22.2). Comparing age and gender distributions for non-lawyer reports versus those sent by lawyers showed that lawyer reports had missing information in 99% of the reports. The single country with the most reports is USA ($n = 5174$, 17%) as well as 99% of lawyer reports were from the USA.

**Table 1** Characteristics of reported ADRs with metoclopramide as suspected or interacting medicine in Vigibase®. Lawyer reports (excluded in study) and non-lawyer reports (included in study) are shown separately

| | Lawyer reports<br>*n* = 16,885<br>*n* (%) | Non-lawyer reports<br>*n* = 30,522<br>*n* (%) |
|---|---|---|
| ADR characteristics | | |
| Most common ADR (SOC level)* | | |
| Neurological disorders | 16,789 (99.4) | 17,214 (56.4) |
| Psychological disorders | 4304 (25.5) | 5519 (28.1) |
| Body as whole—general disorder | 4311 (25.5) | 3579 (11.7) |
| Most common ADR (PT level)* | | |
| Extrapyramidal disorders | 23,352 (73.2) | 5297 (17.4) |
| Tardive dyskinesia | 15,174 (89.9) | 1332 (4.4) |
| Dystonia | 66,003 (39.1) | 2839 (6.0) |
| Time to onset (days) | | |
| 0–5 | 29 (0.17) | 15,866 (52.0) |
| 6–21 | 1 (0.01) | 1142 (3.7) |
| 22–84 | 1 (0.01) | 566 (1.9) |
| > 84 | 18 (0.11) | 555 (1.8) |
| Missing | 16,836 (99.7) | 12,393 (40.6) |
| Population characteristics | | |
| Patient age (years) in gender groups | | |
| Girls 0–17 | 1 (0.01) | 2734 (9.0) |
| Boys 0–17 | 0 (0) | 2116 (6.9) |
| Women 18–44 | 8 (0.05) | 7741 (25.4) |
| Men 18–44 | 6 (0.04) | 3092 (10.1) |
| Women ≥ 45 | 69 (0.41) | 6283(20.6) |
| Men ≥ 45 | 33 (0.20) | 3443 (11.3) |
| Missing age or gender | 16,768 (99.3) | 5113 (16.8) |
| Report characteristics | | |
| Reporting region | | |
| France | 0 (0) | 2919 (9.6) |
| The Nordic countries | 4 (0.02) | 766 (2.5) |
| The rest of Europe | 0 (0) | 4720 (15.5) |
| USA | 16,880 (99.9) | 5174 (17.1) |
| The rest of the World | 1 (0.01) | 16,943 (55.5) |
| Reporting year[1] | | |
| 1968–1988 | 0 (0.0) | 3679 (12.1) |
| 1989–July 2009 | 83 (0.49) | 10,123 (33.2) |
| August 2009–2013 | 15,796 (93.6) | 8928 (29.3) |
| 2014–April 2016 | 1006 (6.0) | 7792 (25.5) |

*ADR characteristics include the three most common ADRs on SOC and PT level. Because one report may contain multiple ADRs, percents may not sum to 100

[1] Selected based on timing of official warnings: The FDA warning was announced July 2009 and EMA warning was announced December 2009

## Proportional reporting ratios

Examining the PRRs shows that the reporting of neurological ADRs is higher for metoclopramide than other medications in Vigibase® for all age-gender groups. PRR was highest for children 0–17 years (4.25 in girls and 4.60 in boys). Women of reproductive age (18–44 years) reported a three times higher proportion of neurological ADRs (PRR = 2.88). This was slightly higher than for women 45 years and older (PRR = 2.16) and men 45 years and older (PRR = 2.36) but slightly lower than men in reproductive age (PRR = 2.99). Examining the PRR for tardive dyskinesia suggests that older adults reported over 40 times higher proportion of TD, regardless of gender, while younger women consistently reported

TD more commonly for metoclopramide than other medications, relative to similar-aged men (PRR 22.2 vs. 9.28) (Table 2).

### Time to onset

TTO was reported for 59.4% (18,129 out of 30,522) of reports (Fig. 1). These reports were used in the Cox regression. The results showed that women and men over 45 years have a lower HR than younger women and men when including all ADR reports (HR = 0.86 for women and HR = 0.79 for men), indicating that this group reported longer time to event onset after treatment initiation. Similar trends were seen for neurological ADRs (HR = 0.84 and HR = 0.79 for women and men 45 years and older, respectively) (Table 3). The trend was especially marked for TD reports, but due to small sample size, we have not presented effect estimates for these analyses.

The time to onset is similar for non-neurological and neurological ADR reports. In general most reported ADRs occur within the first few days of metoclopramide use. Across all age and gender groups, we found that 87.5% of ADRs occurred on or before 5 days after treatment initiation and 3.1% occurred after 12 weeks. The median time-to-onset for the total population was 1 day. This pattern was similar for women aged 18–44, with 90.9% of all ADRs (94.4% of neurological ADRs) occurring on or before 5 days after treatment initiation and 2.4% of all ADRs (1.2% of neurological ADRs) occurring after 12 weeks. For patients older than 45 years, there is a slightly lower proportion of reports with a short TTO (81.4 and 77.7% of reports occur on or before 5 days for women and men, respectively). For tardive dyskinesia, the reported time to onset is much longer in the 45 years and older group where most reports occur (252 out of 460 reports with reported age and gender): only 44.4% of TD cases occur within the first 100 days of treatment for men, and 64.1% for women (Fig. 2).

### Reporting frequency before and after warnings

We compared the percentages of reports coming from each of the regions each year and found wide variation over time and between regions (Fig. 3). After excluding reports from lawyers, reports from the USA increased over time leading to a sharper increase after 2009, peaked in 2012, and declined thereafter. Reports from Europe showed a similar increase, particularly from 2012 onwards (just before the EMA warnings), although this was complicated by a very high peak in 2006 (largely driven by reports from France) and a small decline in 2015.

## Discussion

Our study is, to the best of our knowledge, the first to investigate the time to onset of ADRs associated with use of metoclopramide, and to compare proportional reporting ratios between age and gender groups. We found small differences in reported TTO between age groups, which were largest for tardive dyskinesia, with reported TTO being longer for older individuals. We found no differences between men and women. In addition, we found qualitatively different reporting rates before and after the issue of FDA and EMA warnings related to metoclopramide.

The observed differences in TTO for older vs younger persons could be due to the different indications (leading to different treatment length) for which metoclopramide is used (e.g., chemotherapy related nausea in older adults vs migraine associated nausea and nausea in pregnancy in younger adults). However, differences in indications do not explain the larger differences in TTO in the tardive dyskinesia reports, compared to reports of non-TD related ADR. We speculate that TD in the older patients groups could itself have a longer time to onset independent of the cause of the symptoms. TD in elderly

**Table 2** Proportional reporting ratios for neurological adverse drug reactions: metoclopramide vs. all other drugs, $n = 30{,}522$?

| | Tardive dyskinesia | Other neurological ADR (Tardive dyskinesia excluded) |
|---|---|---|
| Age and gender | PRR (95% CI) | PRR (95% CI) |
| Women 0–17 years | 49.9 (35.9–69.4) | 4.25 (4.17–4.34) |
| Men 0–17 years | 29.6 (21.0–41.8) | 4.60 (4.49–4.72) |
| Women 18–44 years | 22.2 (18.2–27.1) | 2.88 (2.82–2.93) |
| Men 18–44 years | 9.28 (6.46–13.3) | 2.99 (2.90–3.08) |
| Women ≥ 45 years | 42.6 (36.7–49.5) | 2.16 (2.10–2.22) |
| Men ≥ 45 years | 41.4 (32.8–52.2) | 2.36 (2.26–2.46) |

*ADR* adverse drug reaction, *CI* confidence interval; *PRR* proportional reporting ratio. Lawyer reports are excluded

**Table 3** Time to onset for all adverse drug reactions, and neurological adverse drug reactions

| Age and gender | All ADRs (n = 16,249) | | | | Neurological ADR (n = 8999)[c] | | | |
|---|---|---|---|---|---|---|---|---|
| | ADR in first 5 days of treatment (N, %)[a] | Median TTO in days (IQR) | Crude HR, 95% CI | Adjusted[b] HR, 95% CI | ADR in first 5 days of treatment (N, %) | Median TTO in days (IQR) | Crude HR, 95% CI (n = 8999) | Adjusted[b] HR, 95% CI |
| Women 0–17 years | 107 (95%) | 1 (0–2) | 1.03 (0.97–1.10) | 1.05 (0.99–1.10) | 59 (96%) | 1 (0–2) | 1.04 (0.97–1.13) | 1.06 (1.00–1.12) |
| Men 0–17 years | 88 (95%) | 1 (0–2) | 1.05 (0.98–1.12) | 1.05 (1.00–1.11) | 51 (96%) | 1 (0–2) | 1.04 (0.96–1.13) | 1.05 (0.98–1.11) |
| Women 18–44 years | 447 (91%) | 0 (0–2) | 1.03 (0.98–1.09) | 1.03 (0.99–1.07) | 162 (94%) | 1 (0–2) | 1.06 (0.99–1.13) | 1.08 (1.02–1.13) |
| Men 18–44 years | 209 (89%) | 0 (0–2) | 1 | 1 | 87 (92%) | 1 (0–2) | 1 | 1 |
| Women ≥45 years | 685 (81%) | 0 (0–3) | 0.86 (0.82–0.91) | 0.84 (0.79–0.89) | 326 (79%) | 1 (0–3) | 0.86 (0.83–0.90) | 0.78 (0.72–0.84) |
| Men ≥45 years | 457 (78%) | 1 (0–4) | 0.79 (0.74–0.84) | 0.79 (0.73–0.85) | 170 (78%) | 1 (0–4) | 0.79 (0.75–0.83) | 0.73 (0.66–0.80) |

*TTO* Time to onset, *ADR* adverse drug reaction, *CI* confidence interval, *IQR* interquartile range, *HR* hazard ratio, *TD* tardive dyskinesia

[a] Percent is calculated within age-gender group; e.g., for all ADRs, 107 women under age 18 had an ADR within the first 5 days of treatment, out of 2016 women (107/2016) × 100 = 95%

[b] Adjusted for reporting region and reporting year

[c] Neurological ADR analyses excluded 191 cases of tardive dyskinesia

*All patients in the "All ADRs" group will get an ADR and all patients in the "Neurological ADR" group will get a neurological ADR at some point. In these analyses, an HR < 1 suggests that events accumulate more slowly in the specified group, while an HR > 1 suggests that events occur more quickly

treated with antipsychotics has been shown to occur after long-term treatment [19].

We also found that the number of metoclopramide ADR reports has increased in the USA after the FDA issued the black box warning in 2009 and in Europe following the 2013 EMA warning. Changes in prescribing patterns could explain changes in ADR reports; however, reporting from the Nordic countries remained relatively stable. [20, 21]. It is also interesting to note that the FDA and EMA warnings have resulted in media attention, as well as advertisements from law firms targeted at patients using metoclopramide, both of which could have influenced the reporting rate. Indeed, a large portion of the results initially included in our study were sent in by lawyers, which has been observed previously [22, 23]. This also could be partly responsible for the increased PRR values we observe for neurological ADRs; however, we saw a similar pattern in the TTO analyses, which excluded lawyer reports and also adjusted for region and year of report.

In this study, neurological ADRs were more often reported for metoclopramide than other medicines. Women and men of reproductive age are more likely to report neurological ADRs than older women and older men, but less likely than children under 18 years. This is in line with the information provided by the manufacturers in Sweden and by EMA stating that neurological side effects are more common among children and adolescents [1, 24]. However, several studies have found that the elderly are at greater risk for TD when using metoclopramide, partly because advancing age itself is a risk factor for TD [25–27]. Previous research has also found that women are at higher risk of developing TD [28]. These differences may be due to the fact that Vigibase® is a spontaneous reporting system: if health care providers, who report

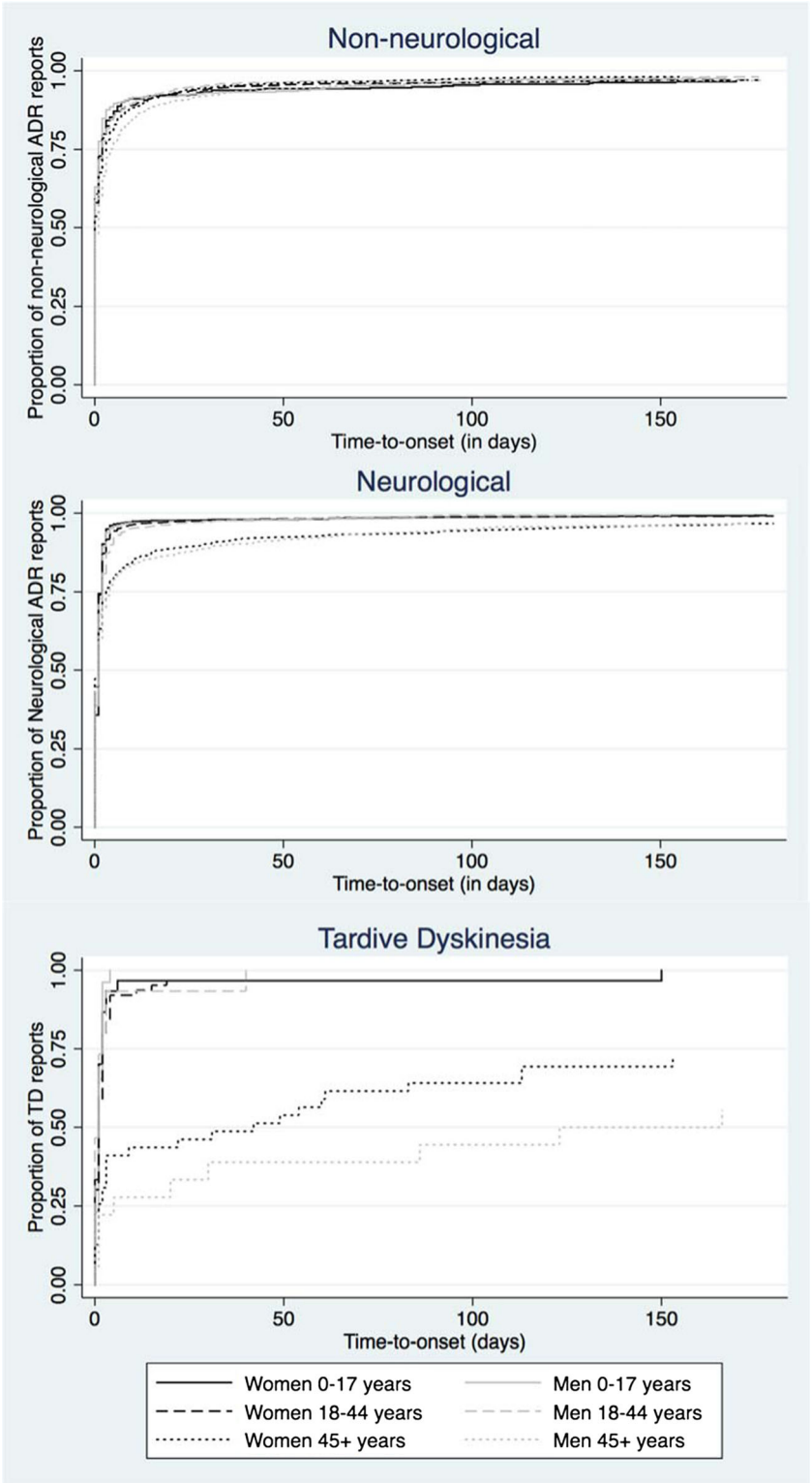


**Fig. 2** Kaplan-Meier failure function with time to onset for adverse drug reports (neurological and non-neurological) with metoclopramide as the suspected or interacting medicine split by age and gender"

ADRs to the system, more often report ADRs that occur unexpectedly (e.g., more often for older than younger patients), they may be over-represented in the data.

Among women of reproductive age, metoclopramide is commonly used to treat nausea and vomiting during pregnancy (NVP) [10, 29]. The required duration of treatment for NVP can sometimes be weeks, and although there are safer agents available as a first choice, metoclopramide offers an alternative to patients for whom other options have not been effective. Our results suggest that patients initiated on

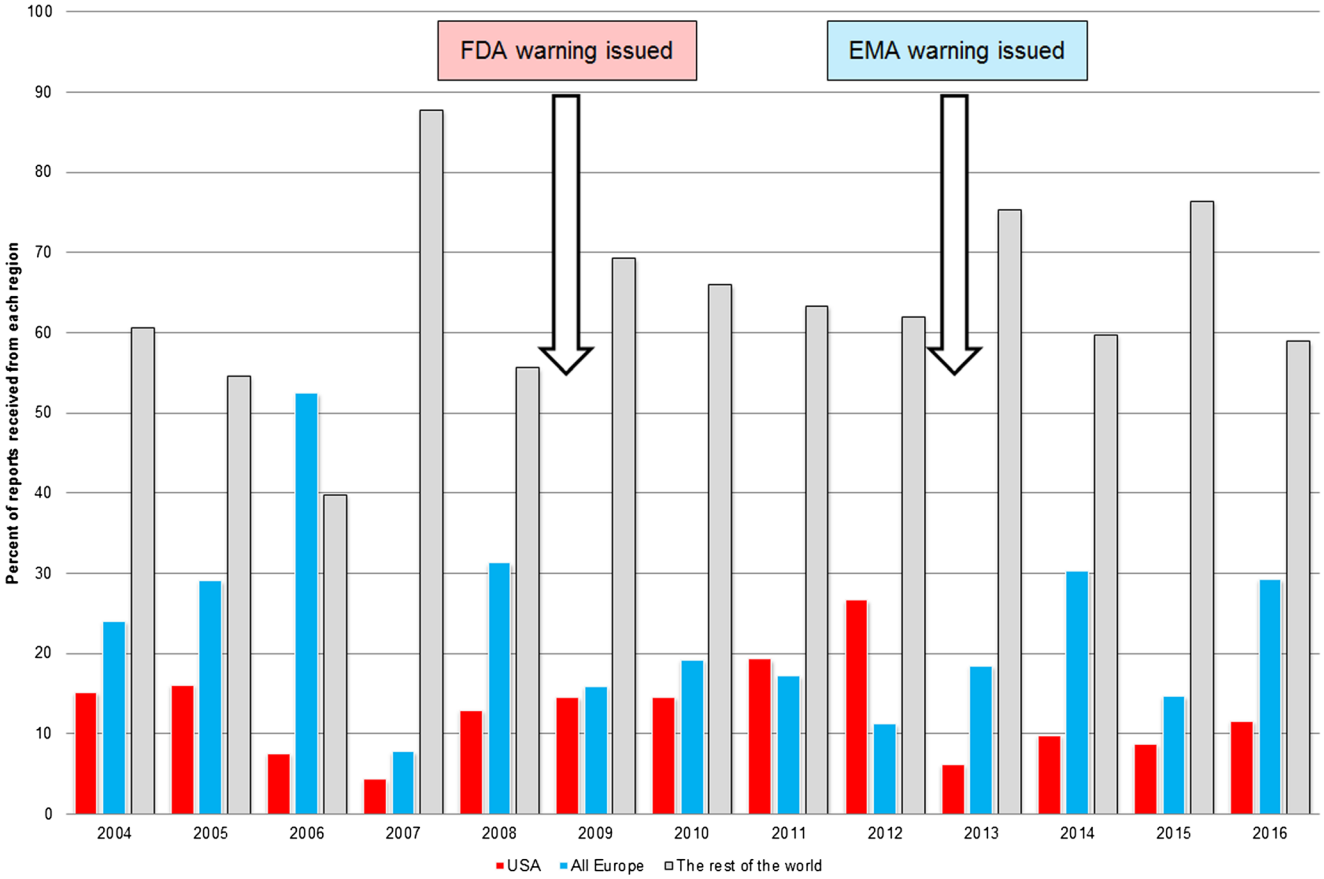


**Fig. 3** Percent of adverse drug reactions reported annually by region, excluding reports from lawyer

metoclopramide should be closely monitored and informed about the symptoms and risks of ADRs during the first few days of treatment, informed about the symptoms and risks of tardive dyskinesia that can occur after longer term treatment, and instructed to use metoclopramide for the shortest possible duration and lowest effective dose as well as contacting health care personnel and stop treatment if ADRs occur.

This study of spontaneous ADR reports has several strengths and limitations. Vigibase® covers 125 different countries and more than 45 years. It is the largest database of spontaneously reported ADRs in the world, containing over 13 million ADR reports. A high number of metoclopramide reports enables multivariable analyses like the ones we have done. However it is also important to consider the limitations with data reported spontaneously. Reactions occurring during active treatment are more likely to be reported than reactions occurring after treatment have been terminated [30], so our short observed TTO can be partially explained by the likely high proportion of short-term use of metoclopramide. It has previously been shown that in spontaneous reporting systems, duration of treatment has a significant impact on the distribution of reported TTO [30] but our data cannot be used to infer anything about the general length of treatment of metoclopramide. The UMC data also does not contain any information about the number of users of metoclopramide in the general population and spontaneous reporting systems are subject to under-reporting of ADRs [31]. This means that the data cannot be used to infer anything about the prevalence of ADRs, or the absolute risk of ADRs associated with metoclopramide use. However, Vigibase® can be used to detect disproportional reporting and signals of specific risks, such as those we report here with neurological ADRs. In addition, because reporting of most information is not mandatory, there is a large amount of missing data, particularly for age and gender, as well as time to onset. If missingness is informative, our results may be biased in unpredictable ways, and caution should be used in interpreting the results. Finally, since the reports in Vigibase® rarely contain information about pregnancy status, we cannot conduct any analyses on risks related to pregnant women specifically.

Clinicians should weigh risks and benefits of metoclopramide treatment in cases of persistent nausea. Both prescribers and policy makers should be aware that, with the exception of TD, most metoclopramide ADRs occur long before the FDA-recommended maximum treatment duration of 12 weeks. More research should be done on the real world

use of metoclopramide in pregnant women, as limitations in Vigibase® data mean that we cannot specifically study this important and vulnerable sub-population.

## Conclusion

Our study found that neurological ADRs are more commonly reported for metoclopramide than for other drugs, and that the average time to onset for ADRs was very short. Older adults more often had longer time to onset than younger adults, regardless of gender. Warnings about metoclopramide use from FDA and EMA occurred during the study period and had marked effects on the number of reports, many of which were sent in by lawyers, rather than patients or healthcare providers.

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### Compliance with ethical standards

**Ethical statement** Since the data received by the UMC is de-identified and furthermore the UMC did not provide any potentially identifiable variables such as narratives or patient initials, no ethical approval was needed.

**Disclaimer** The WHO database contains summary reports of individual suspected adverse reactions to medicines, received from national centers in countries participating in the WHO International Drug Monitoring Programme. No causality assessment is made at the Uppsala Monitoring Centre. Since these reports constitute suspicions of adverse drug reactions, further investigation and research is needed for a full interpretation of the data.

**Conflict of interest** The authors declare they have no conflict of interest.

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