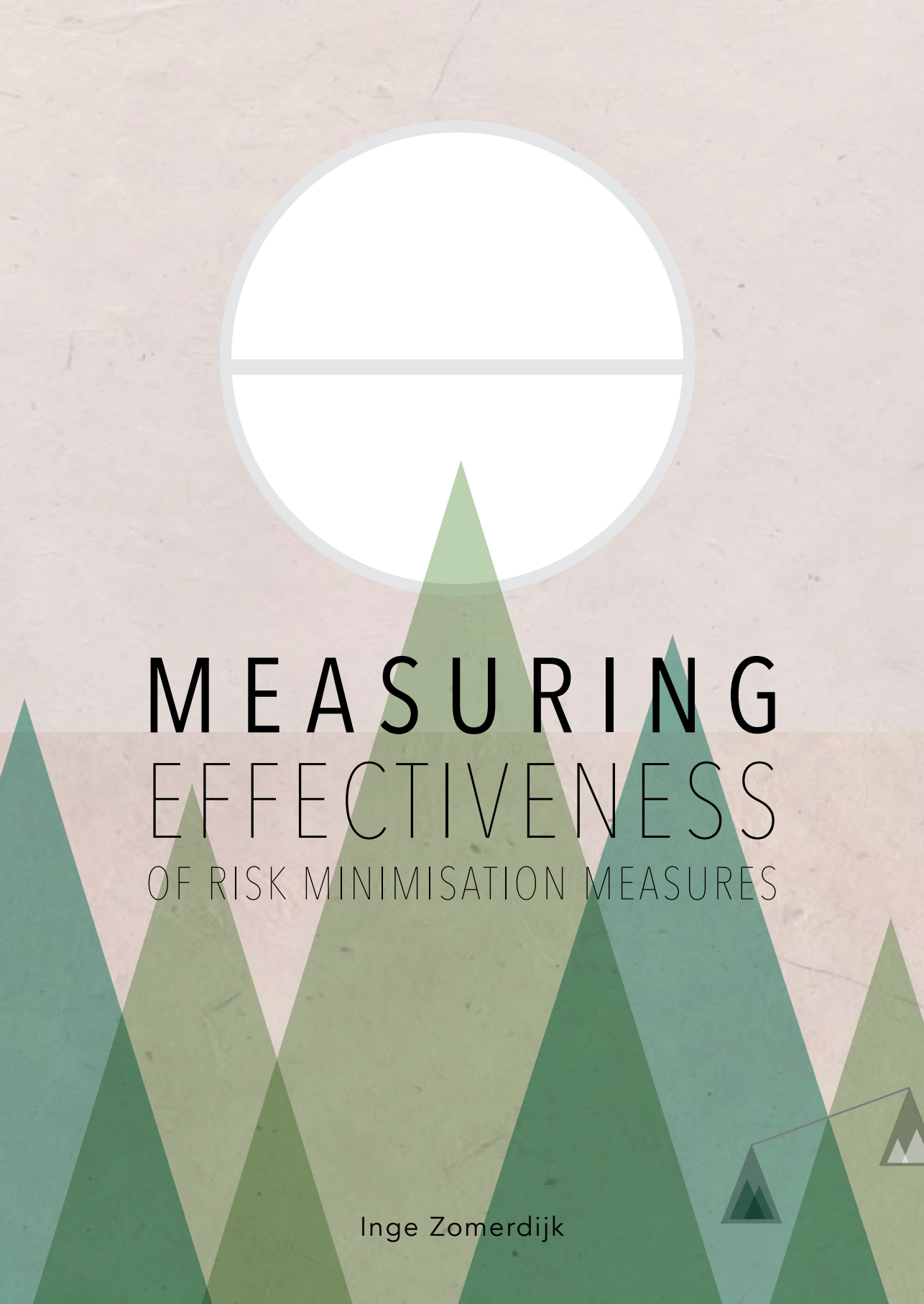

MEASURING EFFECTIVENESS

OF RISK MINIMISATION MEASURES

Inge Zomerdijk

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The work described in this thesis was conducted under the umbrella of the Regulatory Science collaboration between the Dutch Medicines Evaluation Board (CBG-MEB), Utrecht, the Netherlands and the department of Medical Informatics of the Erasmus University Medical Center, Rotterdam, the Netherlands. The CBG-MEB is dedicated to ensure that licensed medicinal products during their whole life cycle have a positive benefit-risk. This role requires intensive collaboration with academic and clinical partners in order to develop new assessment and decision-making methods, to engage with the clinical and to strengthen regulatory science. This thesis aims to go beyond its scientific merits as such by delivering science, learning and insight to promote public health.

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Measuring Effectiveness of Risk Minimisation Measures

Het meten van effectiviteit van risico minimalisatie maatregelen

Proefschrift

ter verkrijging van de graad van doctor aan de
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CONTENTS

1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Knowledge about the benefit-risk profile of a drug is limited at the time of drug approval and grows over time when the drug is increasingly used in routine daily practice. After drug approval the drug is used within a broader and more heterogeneous population with more comorbidities, for a longer period of time and under less controlled circumstances compared with the use during premarketing clinical trials.[1] The dynamics of the benefits and the risks of a drug require a life cycle approach in which the benefit-risk balance is continuously evaluated.[2] Proactive pharmacovigilance is part of the life cycle approach and is aimed at early detection and minimisation of risks.[3] The World Health Organisation (WHO) defines pharmacovigilance as *the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems*.[4] The responsible regulatory authorities at European and Dutch level are the European Medicines Agency (EMA) and the Dutch Medicines Evaluation Board (CBG-MEB), the Netherlands Pharmacovigilance Centre (LAREB) and the Dutch Health Care Inspectorate (IGZ).

Risk minimisation measures

Risk minimisation measures (RMMs) are interventions that aim to optimise the benefit-risk balance of a drug by minimising its risks during drug use in clinical practice. These measures intend to prevent or reduce the occurrence or the severity of adverse drug reactions (ADRs).[5] An adverse drug reaction (ADR) is a response to a drug which is noxious and unintended.[6] This includes events that arise from drug use within the terms of the marketing authorisation but also the use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors. ADRs can be serious and result in hospitalisation, disablement or even death.[7, 8]

RMMs include conditions and restrictions to the drug use in clinical practice to enhance the safe and effective use of a drug. RMMs may be targeted at drug prescription, drug dispensing at the pharmacy as well as preparation and administration of the drug. In addition, RMMs may aim appropriate selection of patients to be treated, appropriate use of the drug by the patient or periodic patient monitoring or examination (e.g. liver function monitoring or electrocardiogram) to early recognise or detect an ADR to timely manage and resolve the event. RMMs are agreed between the marketing authorisation holder (MAH) and regulatory authorities at time of drug registration and may change during the life cycle of the drug for instance when new safety issues emerge. In Europe generally two types of risk minimisation measures can be distinguished, i.e. *routine* risk minimisation measures and *additional* risk minimisation measures (aRMMs). Routine RMMs are required for all drugs and include the Summary of Product Characteristics (SmPC), the patient information leaflet (PIL), the labelling (packaging), the pack size and the legal (prescription) status of a drug.[5] Routine RMMs are usually sufficient; however, some drugs carry serious risks requiring an extra level of risk minimisation, i.e. aRMMs. Examples of aRMMs include educational tools for HCPs or patients, a patient alert card, a pregnancy prevention programme or other controlled access programmes. Controlled access programmes refer to requirements that need to be fulfilled before a drug can be prescribed or dispensed, e.g. specific tests or examinations of the patient, inclusion of the patient in a registry or an informed consent in which the HCP or patient confirms to be aware of certain serious risks and recommendations for use.[5] Examples of drugs with aRMMs in the European Union (EU) are provided in Table 1.

Table 1: Examples of drugs with aRMMs licensed in the EU

Active substance	Therapeutic area	Description of the aRMMs	Risks addressed with aRMMs
Dabigatran	Anticoagulation	Educational programme for HCPs; Patient alert card;	Increased risk of bleeding
Infliximab	Rheumatoid arthritis	Educational programme for HCPs; Pre-treatment tuberculosis testing;	Reactivation of tuberculosis; Opportunistic infections
Lomitapide	Hypercholesterolemia	Educational programme for HCPs and patients; Patient should be included in a registry; Intensive liver function screening;	Appropriate patient selection; Tolerability and gastrointestinal effects; Liver toxicity; Potential teratogenic effects
Insulin degludec 200 units/ml	Diabetes Mellitus	DHPC; Patient brochure; Poster for in pharmacy;	Higher strength available with potential medication error
Bosentan	Pulmonary arterial hypertension	Educational programme for HCPs and patients; Patient alert card; Regular blood test;	Hepatotoxicity; Potential teratogenic; Decrease in haemoglobin

aRMM=additional risk minimisation measures; DHPC=Direct Healthcare Professional Communication; EU=European Union; HCPs=healthcare professionals

In the United States (US) different legal bases are in place but measures comparable to aRMMs in the EU can be required to minimise drug related risks. On a case-by-case basis the Food and Drug Administration (FDA) requires risk evaluation and mitigation strategies (REMS) as part of the marketing authorisation in the US.[9] REMS can consist a Medication Guide, a Communication Plan, Elements To Assure Safe Use (ETASU), an Implementation System and a Timetable for Submission of Assessments.[10]

Risk management plan

In the EU the risk management approach, as part of proactive pharmacovigilance, started with the introduction of the risk management plan (RMP) in 2005. A RMP is an instrument for the planning of pharmacovigilance activities and risk minimisation measures.[11] It allows regulators to specify conditions and restrictions necessary for safe and effective use of the drug in clinical practice, i.e., aRMMs, a possibility that did not exist earlier. For all new active substances approved after 2005 a RMP is in place and the need for aRMMs has been assessed. This has been done on a case-by-case basis, meaning that every single drug is assessed individually and aRMMs can be adapted to drug specific risks and to the context of drug use. Since aRMMs can be required during the entire life cycle of a drug, these additional measures can also be required for drugs that are already on the market.

The risk management approach has become more prominently embedded in the EU Pharmacovigilance legislation operational since July 2012.[6, 12] New regulatory guidelines on the RMP and risk minimisation measures were developed.[5, 13] Once a drug requires aRMMs, the MAH and regulatory authorities agree on the general key elements of the aRMMs. These often are 'Conditions and restrictions with regard to the safe and effective use of the medicinal product' to be implemented by the MAH and valid in all EU member states. Since there can be variation across countries in national legislation, healthcare systems, daily routine care, language and patients' attitudes, the actual implementation of aRMMs

usually occurs at national level with some flexibility to adapt the aRMMs to the local situation. The most important stakeholders in the development and use of aRMMs in clinical practice are described in Table 2.

Table 2: Stakeholders of additional risk minimisation measures

Pharmaceutical industry	The MAH of a drug is responsible for the development of the final aRMMs. The aRMMs need to be developed based on pre-defined key elements of aRMMs and agreed with regulatory authorities. The MAH is also responsible for the implementation and monitoring of the aRMMs in clinical practice following the agreed schedule.
Regulators	As part of the continuous evaluation of the benefit-risk balance of a drug, regulatory authorities assess the need for aRMMs. If needed, key elements of the aRMMs are drafted which need to be translated to final aRMMs by the MAHs.
Healthcare professionals	These can include physicians, pharmacists and other healthcare providers such as nurses. These stakeholders need to work with the aRMMs in daily practice. HCPs can be consulted within the assessment of aRMMs.
Patients	The patients should benefit from the implemented aRMMs by safe and effective use of the drug in clinical practice.

aRMMs=additional risk minimisation measures; HCPs=healthcare professionals; MAH=marketing authorisation holder

Pregnancy prevention programme

For highly teratogenic drugs such as isotretinoin and thalidomide a pregnancy prevention programme (PPP) can be required.[14, 15] Teratogenicity is a serious risk because use of teratogenic drugs shortly before or during pregnancy can lead to spontaneous abortion or birth defects.[16] Women of reproductive age who start using these drugs should therefore not be and not become pregnant during their treatment. Teratogenic drugs should only be prescribed, dispensed and used according to the conditions of the PPP. Among others, these conditions can include educational tools for HCPs and patients about the teratogenic risks and recommendations for safe drug use, concomitant use of contraceptive measures and exclusion of pregnancy with pregnancy tests before and during treatment on a monthly basis. Limited compliance to the PPP may result in spontaneous and elective abortions and more importantly children with major congenital anomalies. Previous studies showed that in the Netherlands just between 52% and 59% of the female isotretinoin users with reproductive age used hormonal contraceptives.[17, 18] Furthermore, isotretinoin-exposed pregnancies do still occur in several Western countries.[19, 20] This emphasizes the ongoing need to evaluate the implementation and compliance to the conditions of the PPP, to identify deficiencies and adapt these measures when considered necessary.

Need to measure effectiveness of risk minimisation measures

Monitoring the outcome of RMMs has become mandatory with the EU Pharmacovigilance legislation effective since July 2012.[6, 12] Besides the planning and implementation of RMMs, the assessment of their effectiveness is a key element of proactive pharmacovigilance and risk management during the life cycle of a drug. Knowledge on how the drug is used in clinical practice and the effects of possible changes in drug use is necessary to evaluate the effectiveness of aRMMs. Several issues limiting the implementation and effectiveness of aRMMs in clinical practice can be identified, requiring adjustment of the implementation or the type of aRMM itself. Furthermore, ineffective measures should not unnecessary burden the health system and should be avoided. The effectiveness of aRMMs might differ across types of aRMM and countries and may also vary among different patient populations.

Additionally, knowledge about successes and failures of aRMMs in specific situations can be helpful for regulators and MAHs to improve effective risk minimisation measures. In the future it might be possible to use these 'best practices' as a reference. Little is known about the implementation and effectiveness of aRMMs nor about the data sources that can be used to measure the effectiveness of aRMMs. Both in the US and the EU some regulatory guidance has become available but this is restricted to very high level recommendations.[5, 10] This points to a substantial need to explore possibilities and challenges of methods that can be used to measure the effectiveness of risk minimisation measures.

Pharmacoepidemiology has been defined as *the study of the use and the effects of drugs in large numbers of people which uses the methods of epidemiology to study the content area of clinical pharmacology.*[21] Often this is done post-licensing in observational settings. While drug utilisation research can provide information on the pattern of drug use over time, across countries, subpopulations and under which conditions the drug is prescribed or dispensed, formal pharmacoepidemiology studies have to be conducted to evaluate the actual minimisation of the risk (e.g. using incidence rates, relative risks, odds ratios). It is known that electronic healthcare databases present opportunities to investigate associations between drugs and adverse events as well as to evaluate drug utilisation patterns.[22, 23] These data sources can contain routinely collected longitudinal data of large patient populations representing actual care including data on clinical diagnosis, test results, drug prescriptions or dispensing and referral data.[24] Examples of databases that can be used to evaluate the use and effects of drugs in clinical practice include primary care medical records, administrative (claim) databases or disease and drug registries. Considering the possible high utility of data available and the efficiency of conducting studies using these data sources, it is relevant to explore whether and how electronic healthcare databases can be used in the evaluation of effectiveness of risk minimisation measures.

Objectives of this thesis

The objective of this thesis is to get insight in the additional risk minimisation measures that are required in the EU and how the effectiveness of these measures can be evaluated. There is a specific focus on the risk minimisation measures of teratogenic drugs (i.e. pregnancy prevention programmes) and exposure to potentially teratogenic drugs in pregnant women.

Outline of this thesis

The first part of the thesis focuses on the description of aRMMs and methods to evaluate the effectiveness of these measures. It starts with an overview of drugs approved for use by the EMA, the so called centrally authorised products. The aRMMs and the corresponding safety concerns of these drugs are presented in **Chapter 2**. After this inventory **Chapter 3** describes which type of aRMMs can be assessed in electronic healthcare databases. With this, the actionable elements of the approved aRMMs as well as the feasibility of electronic healthcare databases in the evaluation of the effectiveness of aRMMs are explored. **Chapter 4** describes the challenges of measuring effectiveness of aRMMs in a post-marketing setting. The possible methodologies involved and difficulties with the interpretation of results are also discussed. In addition, knowledge about evaluating the effectiveness of risk minimisation measures is acquired with a case study. In **Chapter 5** the impact of the recommended dose restrictions for citalopram implemented in October 2011 to minimise the risk on prolonged QT interval during citalopram use is evaluated in two European countries. Two primary care databases are used; The Health Improvement Network (THIN) from the United Kingdom and the Dutch Interdisciplinary Processing of Clinical Information (IPCI).

The second part of the thesis focuses on aRMMs regarding drug exposure during pregnancy. Pregnancy prevention programmes can be required for drugs with high teratogenic risks such as isotretinoin and thalidomide. In **Chapter 6** the different pregnancy prevention programmes that are implemented in the EU are reviewed and compared. The implementation and success of the isotretinoin pregnancy prevention programme in the Netherlands are evaluated in **Chapter 7**. In this population-based study a linkage between the Netherlands Perinatal Registry (PRN) (Dutch birth registry) and the PHARMO Database Network of which the pharmacy dispensing data are used. Using the same cohort of Dutch pregnancies, **Chapter 8** describes the dispensing of potentially teratogenic drugs in the 12-month period before conception or during pregnancy in the Netherlands between 1999 and 2007.

Finally, a discussion on the main findings of this thesis, the lessons learned so far and future perspectives in the area of evaluation the effectiveness of aRMMs is presented in **Chapter 9**.

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2

RISK MINIMISATION ACTIVITIES OF CENTRALLY AUTHORISED PRODUCTS IN THE EU:

A DESCRIPTIVE STUDY

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ABSTRACT

Background Since the new legislation on Risk Management, which came into force in November 2005, an EU Risk Management Plan (EU-RMP) is a required part of the authorisation dossier of innovative drugs licensed in the EU. The EU-RMP can include additional risk minimisation activities (RMAs) to strengthen the benefit-risk balance of a drug. This study describes the additional RMAs of centrally authorised medicinal products authorised between 1 January 1995 and 1 January 2010.

Methods The European Public Assessment Reports (EPARs) of all centrally authorised products were analysed to identify characteristics of the product (active substance, the authorisation date, Anatomical Therapeutic Chemical classification), the additional RMAs and the corresponding safety concerns (classified at Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class level).

Results Additional RMAs were identified for 58 of the 391 active substances that were authorised as of 1 January 2010. The proportion of active substances with additional RMAs was 5% among those authorised before, and 29% among those approved after the new risk management legislation. Since the new legislation, blood products and anti-neoplastic and immunomodulating agents most often had additional RMAs. All active substances with additional RMAs required the provision of educational material, most frequently involving healthcare professionals (n=57) and the patient (n=31). Thirty-three active substances required additional RMAs on top of the provision of educational material, most frequently including patient monitoring and screening (n=19).

Conclusions The proactive pharmacovigilance approach is evolving and the number of products with additional RMAs is growing since the introduction of the EU-RMP. The provision of educational material is the primary additional risk minimisation strategy in the EU. The effect of additional RMA implementation has to be explored.

INTRODUCTION

The knowledge of the full benefit-risk balance of a medicinal product is limited at the time of licensing and can change after approval. For this reason, this balance requires continuous reevaluation during the postmarketing phase when the product is used in clinical practice within a broader and more heterogeneous population compared with premarketing clinical trials.[1] The dynamics of the benefit-risk balance necessitates a life cycle approach with continuous assessment and evaluation of the benefit-risk balance during the whole lifecycle.[2] Proactive pharmacovigilance is part of the life cycle approach aimed at early detection and minimisation of risks, as stated in the strategic plans of European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA).[3, 4]

According to the current EU legislation, in force since November 2005, Marketing Authorisation Applicants (MAAs) have to submit a detailed description of the risk management system as part of the application for drug licensing for innovative products.[5, 6] For new chemical entities, biosimilar medicinal products and generics of substances for which a risk has been identified for the reference product, it is mandatory to submit an EU Risk Management Plan (EU-RMP).[7] Furthermore, an EU-RMP can be requested by regulatory authorities. An EU-RMP consists of a set of pharmacovigilance activities and interventions that are designed to identify, characterise, prevent or minimise the risks during the life cycle of a drug.[6] The EU-RMP aims to ensure that the benefits of a medicinal product exceed its risks to the largest possible extent, both at individual and population level.[7]

For all medicinal products, an EU-RMP includes routine risk minimisation activities (RMA) aiming to reduce the probability or severity of adverse drug reactions (e.g. precautions in the Summary of Product Characteristics [SmPC]). Some medicinal products, however, may carry risks that require an extra level of risk minimisation, i.e. the additional RMAs. Examples of additional RMAs include the provision of educational material, implementation of a pregnancy prevention programme, or intensive monitoring of markers of potential harm, such as liver enzymes for the assessment of hepatic function.[7]

Since 2007 the Food and Drug Administration Amendments Act authorised the FDA to require risk evaluation and mitigation strategies (REMS) as part of the authorisation documents in the US.[3] An REMS can include the following elements: a Medication Guide, a Communication Plan, Elements To Assure Safe Use (ETASU), an Implementation System and a Timetable for Submission of Assessments.[8] A notable difference between the EU and the US is that it is mandatory for the EU-RMPs to be included in the marketing authorisation application for all new active substances and other required situations, while the FDA does not require REMS unless requested on a case-by-case basis. One of the specific challenges for the EU is the variation across countries and the national legislation that is often the main determinant of how additional RMAs are implemented. Since the implementation of the REMS, several studies have described the impact on patients, healthcare providers and health systems in the US.[9-11]

Only a few publications have reviewed EU-RMPs and data on specifically additional RMAs specifically are even more limited.[12-15] To explore the implementation and effectiveness of additional RMAs in the EU, it is necessary to have an overview of the currently approved additional RMAs. The objective of the present study is to describe additional RMAs of medicinal products, which have been licensed through the central authorisation procedure in the EU.

METHODS

Drugs of interest

Centrally authorised products (CAPs) were the medicinal products of interest in this study since information about these products is publicly available. Products authorised through the centralised procedure have a single application, evaluation and authorisation, which is valid throughout the EU market. The centralised procedure was introduced when the EMA was established in January 1995.[16] Although the scope of centralised procedure has been modified over time, the procedure included mainly products derived from biotechnology, officially designated orphan medicines, and those in therapeutic areas of HIV, cancer, neurodegenerative diseases and diabetes mellitus and other innovative products may apply for this procedure.[5, 7] Other terms frequently used within the regulatory field are described in Appendix I.

This cross-sectional study included all active substances authorised through the centralised procedure between 1 January 1995 and 1 January 2010, and which were still authorised as of 1 January 2010. Active substances withdrawn or suspended before 1 January 2010 (n=31) could not be included in our study since limited data regarding these substances was available. Active substance was the basis for the analysis, i.e. substances that were the subject of multiple and/or generic applications and biosimilar medicinal products were only counted once.

Data sources

For each CAP, the European Public Assessment Report (EPAR) is published on the website of the EMA (www.ema.europa.eu) once the medicinal product has a positive decision from the European Commission. The information in the EPAR is updated throughout the lifecycle of the drug and changes to the original terms and conditions of the authorisation (i.e. variations, safety specifications, specific obligations) are included.[17] Since November 2005, the EU-RMP is a mandatory part of the application dossier for drug licensing. The EU-RMP aims to strengthen the benefit-risk balance of a medicinal product by requiring the implementation of routine and additional pharmacovigilance and RMAs (Table 1). Summary information of the EU-RMP is reflected in the EPAR. For each active substance the following characteristics were extracted from the EPAR available as of 1 January 2010: product name(s), Anatomical Therapeutic Chemical (ATC) classification and marketing authorisation date.

Identification of additional risk minimisation activities (RMAs)

A marketing authorisation consists of several parts. If additional RMAs are required, these conditions are laid down in Annexes II and IV of the marketing authorisation. Annex IIB describes specific conditions and restrictions imposed on the Marketing Authorisation Holder (MAH) and Annex IV is addressed to the national authorities of the member states and requires them to ensure that the MAH complies with the conditions or restrictions in their territory. The EMA publishes Annex IIB and IV within the EPAR if special conditions or restrictions have been required. Additional RMAs were considered to be the conditions and restrictions with respect to the safe and effective use of a medicinal product described in these Annexes. Annex IIC of the marketing authorisation, which is also published in the EPAR, describes the specific obligations to be fulfilled by the MAH. To identify the active substances with additional RMAs, Annexes IIB and Annex IV within the EPAR of each active substance available as of 1 January 2010 were analysed. In addition, the Annex IICs of all active substances has been reviewed for additional RMAs to account for the possibility that information might (erroneously) be included in Annex IIC. For active substances with additional RMAs as identified from Annexes IIB, IIC and IV,

Table 1: Structure of the EU-RMP [6, 7, 12, 13]

Part I	
Safety Specification	Summaries the safety profile of a medicinal product at a particular point in time of its lifecycle, including important identified risks, important potential risks and important missing information that could affect the benefit-risk balance of the medicinal product or have implications for public health. It helps to identify the needs for specific data collection and facilitates building of a pharmacovigilance plan and risk minimisation plan
Pharmacovigilance plan	
Routine pharmacovigilance activities	Pharmacovigilance activities that should be conducted for each medicinal product to detect safety signals including the reporting of suspected adverse drug reactions to regulatory authorities, submission of PSURs and other activities as required under EU legislation
Additional pharmacovigilance activities	Activities designed for medicinal product with significant important or potential risks, or significant missing information, in order to detect safety information, e.g. PASSs, clinical trials, monitoring ongoing studies, and registries
Part II	
Evaluation of the need for RMAs	Assessment of each safety concern whether any RMAs are needed beyond the pharmacovigilance plan, and whether routine RMAs will adequately address the safety concern
Risk minimisation plan	
Routine RMAs	Warnings and information within the SmPCs and package leaflet, and the careful use of labelling and packaging, to reduce the probability of an adverse reaction occurring or its severity. The legal status of the product and the pack size are also considered to be routine RMAs
Additional RMAs	Activities that reduce the probability or severity of an adverse drug reaction which go beyond those activities considered as routine. These include educational information for HCPs or patients or through conditions or restrictions that control the use of the medicine or activities for monitoring the patient status

EU-RMP=EU Risk Management Plan; HCPs=Healthcare professional; PASS=Post-Authorisation Safety Study; PSUR=Periodic Safety Update Report; RMAs=Risk Minimisation Activities; SmPC=Summary of Product Characteristics.

the summary information of the EU-RMP was reviewed to obtain detailed information regarding the corresponding safety concerns.

The identified additional RMAs were categorised into six groups, based on the aim and target group of the activity. The additional RMAs are described in Table 2. To explore the effect of the introduction of the EU-RMP on the additional RMAs, the periods before and after the introduction of the new Risk Management legislation (1 November 2005) were analysed separately.

Safety concerns

The safety concerns that required additional RMAs were analysed. The safety concerns addressed by additional RMAs were identified from either the summary information of the EU-RMP or Annexes IIB and IV. These safety concerns were classified based on System Organ Class (SOC) level according to the Medical Dictionary for Regulatory Activities (MedDRA®), version 13.0.18 Safety concerns including specific patient groups e.g. paediatrics or HIV patients, were not included in the MedDRA dictionary

and could not be classified. Therefore, an additional class 'Special patients' was created to review this group separately. Other safety concerns that could not be classified according to MedDRA dictionary (e.g. the term 'long-term safety data') were classified as 'Not Elsewhere Classified' (NEC). If a MedDRA preferred term was related to multiple SOCs, only the primary SOC was considered. A medically trained researcher (IZ) conducted categorisation. In case of doubt, two additional researchers (GT and FST) performed an independent assessment. In case of discrepancy, a fourth expert (SS) arbitrated.

Table 2: Description of the additional risk minimisation activities

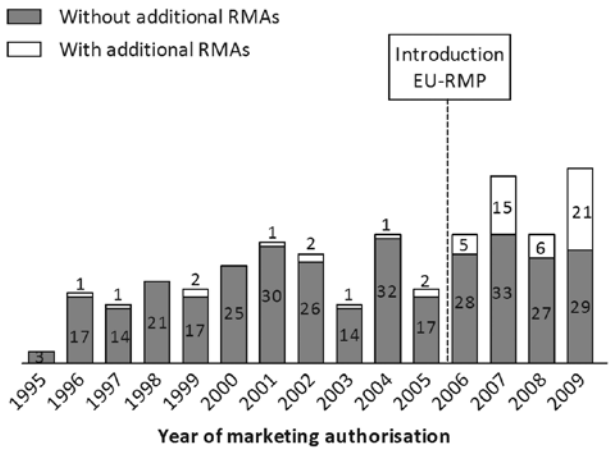
Controlled distribution	Conditions and restrictions at drug distribution level. Distribution is controlled to ensure that certain conditions are met, e.g. medicine is only available in a qualified centre or after a special training programme
Informed consent / treatment initiation forms	Document that ensures that the patient is fully informed of and understands the risk of the medicinal product
Patient monitoring / screening	The need for monitoring of the patient's health status prior or during treatment, e.g. liver function tests, regular blood tests. The need for patient monitoring is highly recommended in Annex IIB of the marketing authorisation, educational material and SmPC, however, it cannot be legally enforced
PPP	A programme, which can contain various elements, that is designed to eliminate the risk of pregnancy during drug exposure
Provision of educational material	The provision of educational material in addition to the SmPC and package leaflet about specific safety concerns (risks) of a drug and measures to reduce these concerns. Educational material could be designed for various target groups (HCPs, patients, laboratories, patient associations etc). Examples of educational material types are DHPC, information brochures and specific training programmes. Various media types (written, audio, video) are possible
Registry	Patient registries to record results of tests, to ensure that the recommended conditions of use are being adhered to, and control access to a medicine. Regularly, registries are considered additional pharmacovigilance activities. However, patient registries acting as additional RMA when it is required for all users of that drug
Special packages / labels	Special packages (i.e. coolboxes) or additional labels (i.e. stickers for traceability of the product), which are required according Annex IIB of the Commission decision, to ensure safe and effective drug use

DHPC=Direct Healthcare Professional Communication; HCPs=Healthcare professional; PPP=Pregnancy Prevention Programme; RMAs=Risk Minimisation Activities; SmPC=Summary of Product Characteristics.

RESULTS

As of 1 January 2010, 391 independent active substances were authorised in the EU through the centralised procedure (Figure 1). For 58 active substances (15%), additional RMAs were identified either in Annex IIB (56 active substances) or Annex IIC (2 active substances) and 43 of these 58 substances (74%) a Commission Decision concerning the additional RMAs addressed to the Member States in Annex IV was identified (see Appendix II).

Figure 1: Active substances with and without additional RMAs per year of marketing authorisation



At the time of the analysis, 5% (11 out of 227) of the active substances, authorised before the new legislation, had additional RMAs, while additional RMAs were identified for 29% (47 out of 164) of the active substances approved after the new legislation. Additional RMAs were most frequently agreed for active substances concerning 'anti-neoplastic and immunomodulating' agents (Figure 2a and b).This was not different for the two periods. In the period after the introduction of the new legislation 50% of the authorised blood products obtained additional RMAs, and 47% of the authorised anti-neoplastic and immunomodulating agents had additional RMAs.

Characteristics of additional RMAs

All active substances with additional RMAs (n=58) required, as a minimum, the provision of educational material (Table 3). Educational material was always directed to healthcare professionals (e.g. Direct Healthcare Professional Communication (DHPC), training programme, brochure), except for one substance (requiring only a patient card). Furthermore, for 53% of the active substances, provision of additional risk information to the patient, such as a leaflet or guide (n=12), a Patient Alert Card (n=13) or both (n=6), was part of the additional RMAs. Of the active substances with additional RMAs, educational material to the patient was required for all substances for the sensory organs (n=2), for 4 out of 5 active substances aimed at treatment of the cardiovascular system, and for the majority of the anti-neoplastic and immunomodulating agents (16 out of 20). In contrast, none of the anti-infective products required the provision of educational material to the patient.

In addition to the provision of educational material, other types of additional RMAs were requested for 57% (33 out of 58) substances (Figure 2a and b). As shown in Table 3, there were 19 active substances with a need for patient monitoring as an additional RMA. This patient monitoring was considered an additional RMA since it was identified from Annex IIB or IIC and not only described in the SmPC, in which case it would have been considered only routine risk minimisation. The need for patient monitoring identified as additional RMA included tuberculosis screening (n=4), regular blood tests (n=7) [e.g. International Normalised Ratio (INR), haemoglobin or haematocrit], liver function monitoring (n=6), and various others (n=9). Active substances with additional need for patient monitoring were in particular interleukin inhibitors (n=3), tumour necrosis factor alpha (TNF-α) inhibitors (n=3), anti-hypertensives indicated for pulmonary arterial hypertension (PAH) (n=3) and products acting on the nervous system

(n=4). Four of the seven anti-infective products with additional RMAs (all vaccines), required a special package or labelling to enable traceability of the batches. The five active substances that required a pregnancy prevention programme also required a controlled distribution system.

Safety concerns

We identified 268 safety concerns addressed by additional RMAs. The provision of educational material addressed 261 of the 268 identified safety concerns (97%) (Table 3). Products with additional RMAs most frequently contained safety concerns, for which additional RMAs were required, classified in SOCs 'general disorders and administration site conditions', 'investigations', 'infections and infestations', and 'injury, poisoning and procedural complications' (Table 4).

Figure 2a: Distribution of active substances authorised before the new legislation on risk managment according to ATC classification system (n=227).

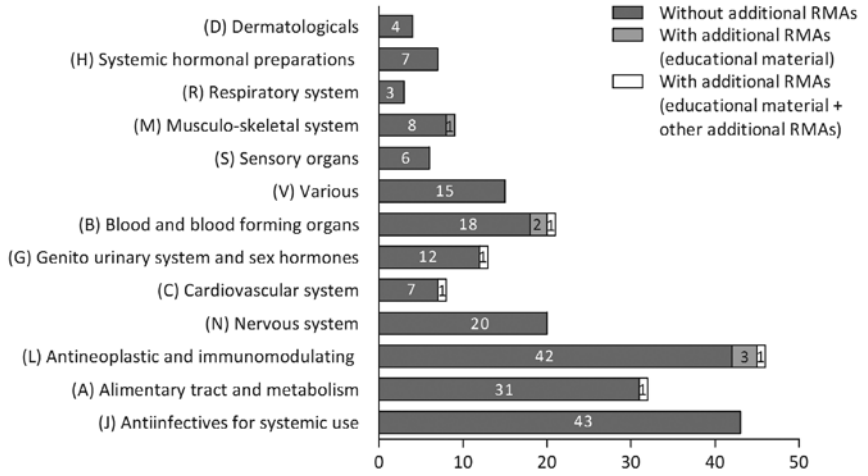


Figure 2b: Distribution of active substances authorised after the new legislation on risk managment according to ATC classification system (n=164).

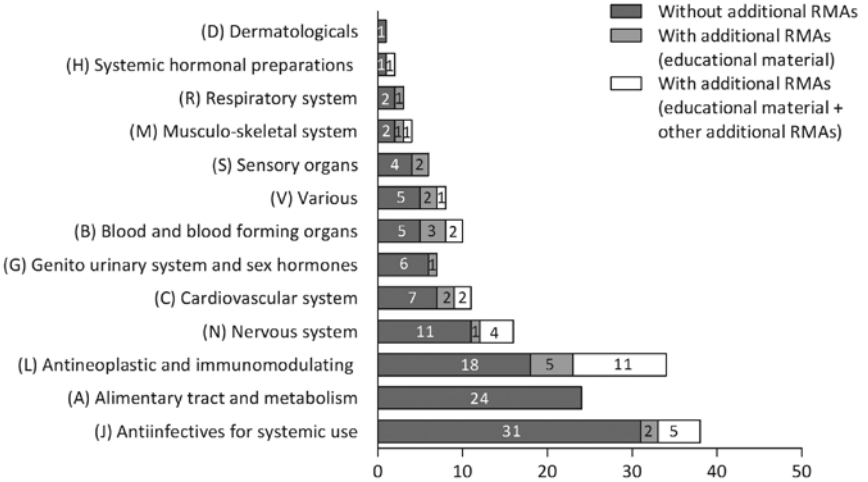


Table 3: Overview of additional risk minimisation activities classified by risk minimisation type

Additional risk minimisation activity	Active substance authorised before new legislation [n=11] (%)	Active substance authorised after new legislation [n=47] (%)	Active substance*	Safety concerns addressed by additional RMAs [n=268]
Provision of educational material – total	11 (100)	47 (100)	All active substances with additional RMAs (Appendix II)	261
to HCPs†	11(100)	46 (98)		251
to the patient	8 (73)	23 (49)		94
Patient monitoring / screening	2 (18)	17 (36)	Agomelatine, Ambrisentan, Bosentan, Caffeine, Canakinumab, Capsaicin, Certolizumab pegol, ChondroCelect®, Deferasirox, Golimumab, Hydroxycarbamide, Infliximab, Mecasermin, Methoxy polyethylene glycol-epoetin beta, Micafungin, Olanzapine, Rilonacept, Sitaxentan, Ustekinumab	43
Controlled distribution	3(27)	7 (15)	5-aminolevulinic acid hydrochloride, Ambrisentan, Bosentan, Caffeine, ChondroCelect®, Eculizumab, Lenalidomide, Miglustat, Sildenafil, Sitaxentan	52
Pregnancy prevention programme	1 (9)	4 (9)	Ambrisentan, Bosentan, Lenalidomide, Thalidomide, Sitaxentan	5
Special packages /labels (e.g. stickers, cool boxes)	1 (9)	6 (13)	Fentanyl citrate, Moroctocog alfa, Pandemic influenza vaccines (Celvapan, Focetria and Pandemrix), Pneumococcal polysaccharide conjugate vaccine, Epoetin alpha	8
Others‡	NA	6 (13)	ChondroCelect®, Clofarabine, Fentanyl citrate, Methoxy polyethylene glycol-epoetin beta, Rinolacept, Thalidomide	17

HCP=Healthcare professional; RMAs=Risk Minimisation Activities.
**authorised before new legislation in italic*
†Prescribers, pharmacists, nurses
‡Informed consent for the patient (n=1), registry (n=1), retesting of the antibody status in a reference laboratory (n=1), single-source distribution (n=1), systematic return of used and unused nasal spray solutions (n=1), treatment initiation form (n=1)

Additional RMAs in addition to educational material were most often required for products with safety issues classified as hepatobiliary disorders (6 out of 7 active substances with hepatobiliary safety issues [86%]), for 83% of the active substances with congenital, familial and genetic safety concerns, for 60% of the active substances with renal and urinary safety concerns and for 50% of the active substances with safety concerns classified as metabolism and nutrition disorders. All safety concerns classified as 'congenital, familial and genetic disorders' were addressed by a pregnancy prevention programme. In addition, 67% of the safety concerns classified as 'infections and infestations' were addressed by the provision of educational material to the patient.

Table 4: Safety concerns of the active substances with additional RMAs classified by System Organ Class

System Organ Class	Active substances with additional RMAs [n=58]	Active substances with additional RMAs on top of educational material [n=33] (57%)*
General disorders and administration site conditions	21	7 (33)
Injury, poisoning and procedural complications	19	6 (32)
Investigations	18	8 (44)
Infections and infestations	14	5 (36)
Blood and lymphatic system disorders	11	5 (45)
Immune system disorders	10	1 (10)
Special patient group	10	2 (20)
Nervous system disorders	10	5 (50)
Neoplasms benign, malignant and unspecified	9	3 (33)
Vascular disorders	9	2 (22)
Cardiac disorders	8	2 (25)
Metabolism and nutrition disorders	8	4 (50)
Surgical and medical procedures	8	2 (25)
Hepatobiliary disorders	7	6 (86)
Congenital, familial and genetic disorders	6	5 (83)
Musculoskeletal and connective tissue disorders	5	2 (40)
Renal and urinary disorders	5	3 (60)
Skin and subcutaneous tissue disorders	5	0 (0)
Pregnancy, puerperium and perinatal conditions	5	1 (20)
Other SOCs†	21	7 (33)

RMAs=Risk Minimisation Activities; SOC=System Organ Class
**Percentage of all active substances with additional RMAs.*
†Include SOCs Not elsewhere classified and SOCs with n < 5 safety concerns (Ear and labyrinth disorders; Eye disorders; Gastrointestinal disorders; Psychiatric disorders; Reproductive system and breast disorders; Respiratory, thoracic and mediastinal disorders).

DISCUSSION

To our knowledge, this is the first descriptive study aimed at exploring additional RMAs among CAPs in the EU. With the new legislation on Risk Management of 2005, the pharmacovigilance of medicines shifted from a largely reactive approach based on the spontaneous reports of suspected adverse drug reactions, to a continuous proactive life cycle management. The EU-RMP is a roadmap that evolves as the benefit-risk profile becomes further defined and additional RMAs facilitate proactive measures to improve the benefit-risk balance.[15] It allows regulatory authorities to specify the conditions and restrictions necessary for the safe and effective use of the medicinal product as part of the marketing authorisation. Before the new legislation this possibility did not exist.

We identified 58 (centrally authorised) active substances with additional RMAs. The proportion of active substances with additional RMAs authorised after the new legislation on risk management is substantially higher as compared to those authorised before the new legislation, 29% and 5% respectively. Comparing the period before and after the new legislation of 2005, the proportion of active substances with additional RMAs varied the most among anti-neoplastic and immunodulating agents. As of 1 January 2010, 9% of these products authorised before the new legislation included additional RMAs, compared to 47% of those that were approved afterwards. This increase is mainly due to the immunosupressants (including selective immunosuppressants, tumor necrosis factor alpha (TNF-α) inhibitors and interleukin inhibitors). Of the immunosupressants authorised before and after the new legislation, 2 out of 11 and 11 out of 12 had additional RMAs respectively.

Although it was not specifically the subject of our analyses, it might be possible that the safety profile of newer products differ from older products, and additional RMAs might be more relevant for these newer products. We observed, however, no substantial changes over the years regarding the most commonly involved product classes of products with additional RMAs. In addition, the proposed additional RMAs of these products were not different, although the number of products with additional RMAs authorised before the new legislation was quite limited.

Since the adoption of legislation, the new proactive approach of pharmacovigilance has gained momentum, and there is increasing awareness of the available options to minimise risks, although we are still at the beginning of realising the full potential of proactive pharmacovigilance.[15] The development towards a more proactive pharmacovigilance with a risk management approach has created additional possibilities for active substances to obtain additional RMAs. In addition, according to the current Guideline on risk management systems, the MAH should justify that there is no need for additional RMAs, suggesting that additional RMAs are needed by default.[7] This might lead, on the one hand to more proposals and, on the other hand, to fewer rejections of proposed additional RMAs by the regulators, causing excessive use. Another concern expressed is the use of inappropriate educational material for commercial interests instead of the intended use. Strict monitoring of the additional RMAs should prevent this. Provisions in the new pharmacovigilance legislation that are to be implemented in July 2012 require monitoring the outcome of additional RMAs, which might limit this risk in the near future.

Educational material

Provision of educational material is the predominant strategy in the EU to reduce the probability or severity of an adverse drug reaction. All active substances with additional RMAs required the provision of educational material, which was used to address 97% of the safety concerns. This might be explained by the fact that provision of educational material is a relatively easy risk minimisation strategy, i.e. not

complicated to produce and simple to implement. In the EU, because different healthcare systems are in place, a certain level of flexibility seems important to facilitate national implementation. For this reason, often only key elements to be included in a certain type of educational material are agreed on EU level. However, at the same time the lack of a standardised approach complicates implementation for member states and MAHs, might hamper evaluation of the effectiveness and cause confusion for patients. In addition, educational material may be interpreted by healthcare professionals, due to, for example, glossy appearance, as promotional and may not have been appreciated as risk minimisation. An overload of educational material may result in a less effective risk minimisation or have a deterrent effect.[19, 20]

Although different legal bases to minimise risks are in force in the US, educational material is also the strategy of choice in the approved REMS. This is in line with our findings regarding the EU. As of June 2010, nearly all (119 of the 123) products with approved REMS listed on the FDA website included at least a medication guide for the patient, and 25% of the REMS included a communication plan for the healthcare professional.[20, 21] In the EU, a patient leaflet is provided routinely, whilst, in the US, a medication guide for patients is only required if requested according to the REMS.[22] In the EU, the provision of educational material as additional RMA was always aimed at healthcare professionals and at patients in 54% of instances, in addition to the standard patient information leaflet.

In our study, 33 active substances in the EU obtained measures in addition to the provision of educational material, and the need for patient monitoring was the second most frequently identified additional RMA. Little consistency of additional RMAs across similar safety concerns was identified in this study, except for 'teratogenicity', that in all cases was addressed with a pregnancy prevention programme, and 'hepatobiliary disorders' which in four of the seven active substances, was addressed with patient monitoring or screening. This lack of consistency can partly be explained by the case-by-case consideration of each safety concern.[7] This emphasizes that the need for additional RMAs can be very drug specific.

Strengths and limitations of the study

Only CAPs were included in this study, which limits the generalisability of our findings. Active substances authorised through other procedures could have additional RMAs as well since the Guideline on risk management systems applies to all medicinal products.[7] However, additional RMAs are most likely for innovative, complex and technically advanced products, which are generally authorised through the centralised procedure. In view of the type of products authorised through other procedures, e.g. generic medicinal products, very few others would have additional RMAs. One well known example is the pregnancy prevention programme of isotretinoin, which aims to reduce the risk of teratogenicity.[23]

From our cross-sectional analysis it cannot be concluded if an active substance had additional RMAs at time of initial marketing authorisation, or whether these were obtained during post-authorisation. The EU-RMP is not designed as 'on-off', but rather as a continuous process amended as the experience growths and the benefit-risk profile of the drug further evolves.[15] The EPAR can be appropriately adapted during the life-cycle of the drug, with only the most recent version published. The exact timing of additional RMAs coming into force is therefore difficult to assess from publicly available data. This information might be specifically relevant for the active substances authorised before the new legislation on risk management came into force, and which required additional RMAs during the lifecycle.

The EPAR of some products contained discrepancies regarding information on additional RMAs.

Differences between Annex IIB and the summary information of the EU-RMP were observed, in which either of these two documents contained extra additional RMAs. Furthermore, difficulties with the difference between pharmacovigilance activities and additional RMAs were observed in these documents. In some instances, pharmacovigilance activities such as close monitoring of the safety issue in the Period Safety Update Report or long-term safety and effectiveness studies, were presented as additional RMAs. The aim of pharmacovigilance activities essentially differs from additional RMAs; while the former aims to study post marketing safety concerns, the latter aims to reduce the probability of an adverse drug reaction. The discrepancies can easily be explained by a change in the characteristics of EU-RMPs, and the quality of the corresponding summary information of the EU-RMPs and Annexes IIB over time (improvements from learning and interventions), which will reduce the chance of such misclassification in future. The quality of the first EPARs can explain the two active substances with additional RMAs described in Annex IIC instead of Annex IIB. We might have missed active substances with additional RMAs, of which details regarding additional RMAs were lacking in the EPAR. We agree, in line with previous studies, that the quality of the publicly available information regarding additional RMAs should be improved.[12, 13] A possible solution might be to provide a periodic overview of the required additional RMAs, including changes over time and updates of the EU-RMP regarding both additional pharmacovigilance and additional RMAs.

Giezen et al.[13] evaluated post-authorisation safety studies (PASS) as part of the EU-RMP. The authors observed limited availability of full/partial study protocols of the PASS, precluding a scientific assessment of these studies at time of regulatory approval. In line with previous findings, also in our study, limited availability of comprehensive information concerning additional RMAs precluded an in-depth description of the additional RMAs and the corresponding risks. Although all stakeholders, including healthcare professionals, have theoretically full access to product information (including annex IIB) and public assessment reports of the CAPs via the EMA website, it is a challenge to find information and instructions regarding the additional RMAs, e.g. which medicinal products require special obligations or restrictions and the type of measures involved. More transparency and easier access to information concerning additional RMAs, the corresponding risks and the evaluation of the need for additional RMAs may enhance awareness of the role that these activities have in clinical practice and might facilitate implementation at the national level. Equal critical points were identified by Frau et al.[12] The authors identified limited transparency as one of the main issues that influences adequate implementation of EU-RMPs. We agree with the authors that better access to pharmacovigilance activities and doctor and patient programmes is needed to improve the effect of the additional RMAs.

Implications

Since 2005, the growing experience on the EU-RMP and the additional RMAs has led to a better understanding of the possibilities and challenges of this proactive approach. The EU-RMP offers knowledge gain regarding the drug's benefit-risk profile and possibilities to ensure safe drug use during the product lifecycle. The new pharmacovigilance legislation that will come into force mid-2012 will further broaden the opportunities. There will be major changes to existing processes in the member states, the EMA and MAHs with regard to evaluation of risks associated with medicinal products. In addition, the framework on how the EU takes harmonised regulatory action on drug safety needs to implemented in July 2012.[24]

The full opportunities offered by the EU-RMP are only beginning to be appreciated and challenges concerning the implementation and the assessment of effectiveness of additional RMAs will need to be further addressed. Actual implementation of the additional RMAs takes place at national level and

has to take into account national requirements e.g. health systems, language and health believes. This national phase allows the realisation of better fitting programmes and better compliance of the healthcare professionals and patients, which in turn might positively influence the effects of additional RMAs. Additional RMAs put an extra burden on the system and should therefore not only be carefully drafted and monitored, but also only requested if added value of the benefit-risk balance is to be expected. It is in the interest of patients, healthcare professionals, industry and regulators that the least harm and the maximum benefit results from using a medicine, and to avoid unnecessary, inefficient measures.

Recommendations in the new pharmacovigilance legislation offer opportunities to better address the limitations of the current guidance since it requires the EMA, the member states and the MAHs to monitor the outcome of additional RMAs.[25, 26] Knowledge regarding the effectiveness of additional RMAs will impact the drafting and implementation of additional RMAs and will, in future, lead to improved benefit-risk balance and increased patient safety. Currently there is limited knowledge available regarding the effectiveness of additional RMAs.[27-32] In view of the new pharmacovigilance legislation, methods to evaluate the implementation and effectiveness of additional RMAs need to be developed. In addition, it will be relevant to study the implementation of the additional RMAs and have a closer look at the differences across countries and the influences on the individual patient safety.

Conclusions

This study describes the additional RMAs of CAPs that are required to be implemented when the drug has been, or will be, marketed in an EU member state. The risk management approach is developing and the number of products with additional RMAs is growing after the introduction of the EU-RMP. Almost one third of the recent CAPs required additional RMAs, which emphasised the need for evaluation of these measures. Future research should explore the effects of additional RMA implementation in the minimisation of risks associated with drug therapies in EU at both patient and population level

Appendix I: Short description of terms frequently used within the regulatory field of medicines evaluation

Term	Description
ATC classification system	This drug classification system divides the active substances into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. The classification system is controlled by the WHO Collaborating Centre for Drug Statistics Methodology[18]
Annex IIB	The EMA publishes Annex IIB of the European Commission Decision in the publicly available EPAR to present the conditions imposed on the MAH. Annex IIB includes the conditions or restrictions imposed on the MAH, with regard to the safe and effective use of the medicinal product which reflect the additional RMAs approved for the product
Annex IIC	The EMA publishes Annex IIC of the European Commission Decision in the publicly available EPAR to present the specific obligations to be fulfilled by the MAH. Specific obligations data to be submitted in the post-authorisation phase are specific to marketing authorisations granted under exceptional circumstances due to limited efficacy and/or safety data available at the time of the CHMP opinion
Annex IV	In addition to Annex IIB, the EMA may publish Annex IV of the European Commission decision. This is a decision addressed by the Commission to the national authorities of the EU member states and contains conditions or restrictions with regard to the safe and effective use of the medicinal product. Annex IV of the Commission Decision requires the national authorities to ensure that the MAH implements the additional risk minimisation activities in their territory
Biological medicinal product	Biological medicines are made by a living organism, such as a bacterium or yeast, and can consist of relatively small molecules such as human insulin or erythropoietin or complex molecules such as monoclonal antibodies[33]
Biosimilar medicinal product	A 'biosimilar' medicine is a biological medicine that is similar to another biological medicine (the 'biological reference medicine') that has already been authorised for use[33]
Centralised authorisation procedure	The EMA is responsible for the centralised authorisation procedure. It is a registration procedure for which a single application and evaluation, if positive, results in a single marketing authorisation applicable to the whole EU. The centralised procedure includes mainly medicinal products derived from biotechnology, for officially designated 'orphan medicines', for those in certain therapeutic areas (HIV, cancer, neurodegenerative diseases, diabetes mellitus, immunosuppressive diseases and viral diseases) and is available for other innovative products[5]
CMDh	The CMDh is the co-ordination group of the EMA and examines questions relating to the marketing authorisation of a medicinal product for human use in two or more Member States in accordance with the mutual recognition procedure or the decentralised procedure[5]
CHMP	The CHMP is the scientific Committee of the EMA and is responsible for providing the European Commission with a scientific opinion on the quality, safety and efficacy of the medicinal product, especially with regard to centralised authorisation procedures. The members and alternates of the CHMP are nominated by the EU Member States, based on their individual expertise[5]
European Commission decision	In case of marketing application, the CHMP's opinion is transmitted to the European Commission which gives a decision. If the Decision is positive, the MAA can grant a marketing authorisation[5]
EMA	The EMA is a decentralised body of the EU located in London and was established under Regulation 2309/93 EC to harmonise the work of national medicine regulatory bodies. It came into being in January 1995. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use[16]

Appendix I: Short description of terms frequently used within the regulatory field of medicines evaluation

Term	Description
EPAR	The scientific grounds for the CHMP opinion concerning the approval of a medicinal product are reflected in the EPAR, which includes the product information (SmPC, labelling and package leaflet) for the medicine, details of the procedural steps taken during the assessment process and the CHMP Assessment Report with confidential parts removed. The EPAR of all centrally authorised products are published on the EMA website[17]
Generic medicinal products	Once the 10-year data protection of a medicinal product expires, another MAA can apply for a marketing authorisation for a generic medicine. A generic medicinal product is equivalent to the original medicinal product, since the generic medicinal product contains the same active substances at the same concentration and has similar therapeutic efficacy and safety as the original medicinal product[5]
Life cycle approach	The continuous evaluation and integration of drug safety and efficacy during the entire lifecycle of a drug. After approval, when the drug is used within a broader population, benefit-risk assessment with post-authorisation data is an ongoing activity[1, 2]
Multiple applications	A term used when MAAs wish to obtain, either simultaneously or successively, more than one marketing authorisation for a specific medicinal product, under different invented names[5]
Pharmacovigilance	Pharmacovigilance is defined by the WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem[34]
PhVWP	PhVWP is a working party of the CHMP, which provides recommendations to the CHMP on the safety of medicinal products and on the investigation of adverse reactions associated with medicinal products authorised in the EU and other issues relating to pharmacovigilance[35]
REMS	The FDA Amendments Act of 2007 has given the FDA the authority to require a REMS from MAAs to ensure that the benefits of a drug or biological product outweigh its risks. REMS contain an analysis of possible risks and measures to mange known or expected safety issues[3]
EU-RMP	The EU-RMP describes the risk management system of a medicinal product, which is a required part of certain applications for drug licensing. This requirement was part of the new legislation which came into force in November 2005. It is mandatory to submit an EU-RMP for new chemical entities, biosimilar medicinal products and generics of substances for which a risk has been identified for the reference product. Furthermore, it can be requested by regulatory authorities.[5, 7] See Table 1 for a further description of the EU-RMP
US FDA	The FDA is responsible for protecting public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics, products that emit radiation, and tobacco products. In addition, the FDA is responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health[36]

ATC=Anatomical Therapeutic Chemical; CHMP=Committee for Medicinal Products for Human Use; CMDh=Co-ordination Group for Mutual Recognition and Decentralised Procedures – human; EMA=European Medicines Agency; EPAR=European Public Assessment Report; EU-RMP=EU Risk Management Plan; FDA=Food and Drug Administration; MAAs=Marketing Authorisation Applicants; MAH=Marketing Authorisation Holder; PhVWP=Pharmacovigilance Working Party. REMS=Risk Evaluation and Mitigation Strategy; RMAs=Risk Minimisation Activities; SmPC=Summary of Product Characteristics.

Appendix II: Centrally authorised active substances with additional RMAs in the EPAR at 1 January 2010

Active substance	Product name	ATC code	Date of issue of marketing authorisation	Annex
5-aminolevulinic acid hydrochloride	Gliolan®	L01XD04	07-Sep-07	IIB + IV
Abatacept	Orencia®	L04AA24	21-May-07	IIB
Adalimumab	Humira®	L04AB04	08-Sep-03	IIB
Agomelatine	Thymanax®, Valdoxan®	N06AX22	19-Feb-09	IIB + IV
Alemtuzumab	MabCampath®	L01XC04	06-Jul-01	IIB + IV
Ambrisentan	Volibris®	C02KX02	21-Apr-08	IIB + IV
Anidulatungin	Ecalta®	J02AX06	20-Aep-07	IIB
Bosentan	Tracleer®	C02KX01	15-May-02	IIB + IV
Caffeine citrate	Nymusa®	N06BC01	02-Jul-09	IIB + IV
Canakinumab	Ilaris®	L04AC08	23-Oct-09	IIB + IV
Capsaicin	Qutenza® (Transacin)	N01BX04	15-May-09	IIB
Certolizumab	Cimzia®	L04AB05	01-Oct-09	IIB + IV
Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	ChondroCelect®	M09AX02	05-Oct-09	IIB + IV
Clofarabine	Evoltra®	L01BB06	29-May-06	IIC
Deferasirox	Exjade®	V03AC03	28-Aug-06	IIB + IV
Degarelix	Firmagon®	L02BX02	17-Feb-09	IIB + IV
Dronedarone	Multaq®	C01BD07	26-Nov-09	IIB + IV
Eculizumab	Soliris®	L04AA25	20-Jun-07	IIB + IV
Efavirenz/emtricitabine/tenofovir disoproxil	Atripla®	J05AR06	13-Dec-07	IIB
Epoetin alfa	Abseamed®, Binocrit®, Epoetin alfa Hexal®	B03XA01	28-Aug-07	IIB + IV
Epoetin zeta	Retacrit®, Silapo®	B03XA01	18-Dec-07	IIB + IV
Eptacog alfa (activated)	NovoSeven®	B02BD08	23-Feb-96	IIB + IV
Eptotermin alfa	Opgenra®	M05BC02	19-Feb-09	IIB + IV
Fentanyl citrate	Instanyl®	N02AB03	20-Jul-09	IIB + IV
Gadoversetamide	OptiMARK®	V08CA06	23-Jul-07	IIB
Golimumab	Simponi®	L04AB06	01-Oct-09	IIB + IV
Hydroxycarbamide	Siklos®	L01XX05	29-Jun-07	IIB + IV
Indacaterol	Hirobriz Breezhaler®, Onbrez Breezhaler®, Oslif Breezhaler®	R03AC18	30-Nov-09	IIB
Infliximab	Remicade®	L04AB02	13-Aug-99	IIB + IV
Lasofoxifene	Fablyn®	G03XC03	24-Feb-09	IIB + IV
Lenalidomide	Revlimid®	L04AX04	14-Jun-07	IIB + IV
Mecasermin	Increlex®	H01AC03	03-Aug-07	IIB + IV
Methoxy polyethylene glycol-epoetin beta	Mircera®	B03XA03	20-Jul-07	IIB + IV
Micafungin (as sodium salt)	Mycamine®	J02AX05	25-Apr-08	IIB + IV
Miglustat	Zavesca®	A16AX06	20-Nov-02	IIC
Moroctocog alfa	ReFacto AF®	B02BD02	13-Apr-99	IIB + IV
Natalizumab	Tysabri®	L04AA23	27-Jun-06	IIB + IV
Nilotinib	Tasigna®	L01XE08	19-Nov-07	IIB + IV
Nonacog alfa	BeneFIX®	B02BD09	27-Aug-97	IIB

Active substance	Product name	ATC code	Date of issue of marketing authorisation	Annex
Olanzapine (as pamoate monohydrate)	Zypadhera®	N05AH03	19-Nov-08	IIB + IV
Pandemic influenza vaccine	Celvapan®	J07BB01	04-Mar-09	IIB
Pandemic influenza vaccine	Focetria®	J07BB02	02-May-07	IIB
Pandemic influenza vaccine	Pandemrix®	J07BB02	20-May-08	IIB
Pegaptanib sodium	Macugen®	S01LA03	31-Jan-06	IIB + IV
Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar 13®	J07AL02	09-Dec-09	IIB
Porfimer sodium	PhotoBarr®	L01XD01	25-Mar-04	IIB + IV
Prasugrel	Efient®	B01AC22	25-Feb-09	IIB + IV
Ranibizumab	Lucentis®	S01LA04	22-Jan-07	IIB + IV
Ranolazine	Ranexa® (Latixa)	C01EB18	09-Jul-08	IIB + IV
Rilonacept	Arcalyst®	L04AC08	23-Oct-09	IIB + IV
Romiplostim	Nplate®	B02BX04	04-Feb-09	IIB + IV
Sevelamer carbonate	Renvela®	V03AE02	10-Jun-09	IIB + IV
Sildenafil	Revatio®	G04BE03	28-Oct-05	IIB + IV
Sitaxentan	Thelin®	C02KX03	10-Aug-06	IIB
Thalidomide	Thalidomide Celgene®	L04AX02	16-Apr-08	IIB + IV
Tocilizumab	RoActemra®	L04AC07	16-Jan-09	IIB + IV
Ustekinumab	Stelara®	L04AC05	16-Jan-09	IIB + IV
Zoledronic acid	Aclasta®	M05BA08	15-Apr-05	IIB + IV

ATC=Anatomical Therapeutic Chemical; EPAR=European Public Assessment Report; RMAs=Risk Minimisation Activities

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ADDITIONAL RISK MINIMISATION MEASURES IN THE EU: ARE THEY ELIGIBLE FOR ASSESSMENT?

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ABSTRACT

Background Additional risk minimisation measures (aRMMs) can be necessary to optimize the benefit-risk balance of a drug. Evaluation of effectiveness of these measures has become mandatory with the new European Union (EU) pharmacovigilance legislation in force since July 2012. The aim of this study was to classify the aRMMs in the EU with a special emphasis on the possibilities to analyse the effectiveness of these aRMMs in existing electronic healthcare databases (EHDs).

Methods European Public Assessment Reports were reviewed to identify key elements of the aRMMs. Researchers categorised the key elements based on the objectives, i.e. knowledge change or behavioural change and sub-categorised the behavioural changes. They assessed for each key element if it would be eligible for analysis in existing EHDs.

Results 68 drugs with aRMMs contained 801 key elements of which 57% aimed at behavioural changes. 22% of all key elements, all aimed behavioural changes, were assessed eligible for analysis in existing EHDs. These mainly concerned recommendations targeted at healthcare professionals regarding drug prescription, e.g. dose recommendations, contraindications or the need to perform laboratory tests for patient monitoring.

Conclusions Only a limited proportion of key elements of the aRMMs could potentially be monitored in existing EHDs as these data sources cannot capture all the required data. Due to difference between existing EHDs, not necessarily all available EHDs are appropriate for every drug or aRMM. To facilitate rapid evaluation of aRMM implementation and timely adjustments, industry and regulatory authorities should agree well-defined key elements of aRMMs leading to unambiguous actions of the target group.

KEY POINTS

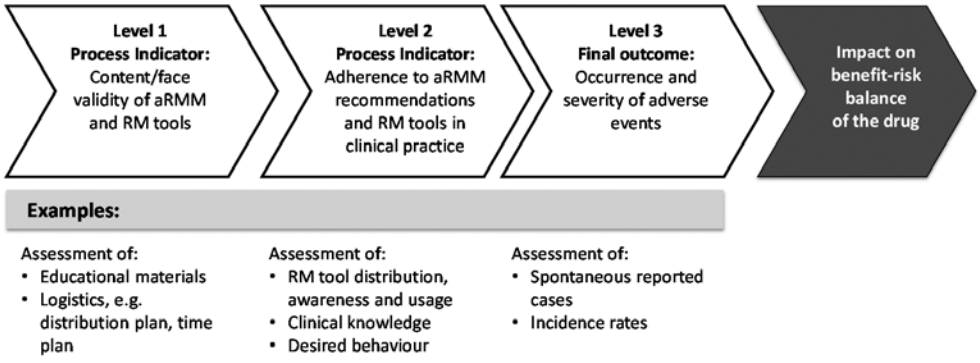
- Measuring the effectiveness of additional risk minimisation measures (aRMMs) is essential in the continuous evaluation of the benefit-risk balance of a drug and recently has become a legal requirement in the EU.
- Rapid aRMMs assessment is necessary to modify aRMMs and improve implementation in an early stage to further optimise the benefit-risk balance of a drug.
- Electronic healthcare databases have been extensively used in pharmacoepidemiology, and may present opportunities to investigate the implementation and performance of aRMMs rapidly.
- Currently, the majority of the aRMMs is however not considered suitable for evaluation in electronic healthcare databases, and it remains a challenge to analyse these aRMMs in an efficient and proper way.
- To facilitate the rapid evaluation of aRMMs and timely aRMM adjustment, it is essential that industry and regulatory authorities agree on well-defined aRMM key elements leading to unambiguous actions of the target group.

INTRODUCTION

Risk minimisation measures (RMMs) are an essential part of life cycle management of a drug. These measures intend to reduce the occurrence of an adverse drug reaction (ADR) or to reduce its severity should it occur.[1] Routine RMMs required for all drugs include the summary of product characteristics, the labelling, the package leaflet, the pack size and the legal status of the drug.[1] Sometimes additional risk minimisation measures (aRMMs) are necessary to optimize the benefit-risk balance of a drug. aRMMs are those measures that go beyond the routine requirements and should only be required to address specific critical safety issues not sufficiently addressed by routine RMMs only.[2] In the European Union (EU) aRMMs are described in the Risk Management Plan (EU-RMP), a mandatory part of a marketing application since the end of 2005.[1, 3] Examples of aRMMs are extra education for healthcare professionals (HCPs) and patients, pregnancy prevention programme and patient screening. aRMMs pose an extra burden on the health system and should therefore be carefully justified, drafted and monitored, and only requested if added value is expected. It is in the interest of patients, HCPs, industry and regulators that the least harm and maximum benefit results from using a medicine, and to avoid unnecessary, ineffective measures.

Proactive and proportionate pharmacovigilance during the life cycle of a medicinal product is firmly embedded in the new European pharmacovigilance legislation effective since July 2012, and monitoring the outcome of RMMs became mandatory for regulators and marketing authorisation holders (MAHs).[4-6] Since these outcomes can impact the benefit-risk balance of drug, evaluation of aRMMs is an essential part of the continuous evaluation of the benefit-risk balance of a drug. Assessment of actual implementation of aRMM in clinical practice is necessary to evaluate whether aRMMs can successfully improve the drug's benefit-risk profile in routine daily care. The evaluation of actual implementation of aRMMs can comprise different elements (Figure 1), including assessment of the effect of aRMM on the clinical knowledge of patients and HCPs as well assessment of desired behavioural changes of HCPs or patients.

Figure 1: Evaluation of risk minimisation measures



aRMM=additional risk minimisation measure; RM=risk minimisation

There is a need for rapid evaluation and timely feedback on the implementation and the effectiveness of the aRMMs to allow adjustment in an early stage. Prospective data collection (e.g. by means of a survey) can be lengthy and unnecessarily delay such an assessment. Since existing electronic healthcare databases (EHDs) present opportunities to investigate rapidly the associations between a drugs and adverse events,[7, 8] it is relevant to explore whether these resources can be used to explore the implementation and performance of aRMMs. However, currently only limited knowledge on how aRMM evaluation can be conducted and on the data sources that can be used for the measurement of the aRMM effectiveness is available.[9, 10]

The aim of this study was therefore to classify the aRMMs of the medicinal products authorised in the EU with a special emphasis on the possibilities to analyse the effectiveness of these aRMMs in existing EHDs.

METHODS

Medicinal products included in this study were the centrally authorised products with aRMMs, authorised as of 1 April 2011. Products authorised before the EU-RMP became a mandatory part of the application in 2005 were included since also for these products aRMMs can be in place. The method for identification of drugs with aRMMs have been previously described.[2] For each drug included in our study the European Public Assessment Report, which is published on the website of the EMA (www.ema.europa.eu), was reviewed to identify key elements. Key elements are those components of aRMMs that are agreed by regulatory authorities at European level and provide guidance for implementation of aRMMs at member state level. For each drug multiple key elements can be agreed, e.g. instructions regarding drug administration; recommendation to monitor creatinine clearance or perform an electrocardiogram. For this study, the key elements of the aRMMs were the unit of analysis.

Categorisation of the key elements

The aRMM key elements were classified by the researchers into ten categories according the objective of the key element. The different categories are described in Table 1. For each key element, the objective was classified as 'knowledge change' or 'behavioural change'. In addition, the target group was identified as 'HCPs' or 'patients'. Key element aiming at behavioural changes in patients were subcategorised in 'recommended actions to be followed during treatment use' (e.g. patient should avoid sunlight exposure) and 'recommended actions to early detect or treat/resolve ADRs' (e.g. patient should contact your doctor when you experience symptoms). Key elements aimed at behavioural changes in HCPs were subcategorised in 'recommended actions regarding drug prescription' (e.g. contraindication or dose recommendations), 'recommended actions regarding the drug administration process' (e.g. patient should lay down during infusion), 'recommended actions to perform clinical examinations or laboratory tests' (e.g. monthly blood tests) and 'recommended actions to treat/resolve ADRs' (e.g. HCPs should stop treatment if bleeding occurs). The key elements that could not be categorised in any of the groups were included in a separate category 'others' (e.g. instructions to immediately report adverse events).

The classification of the key elements in the different categories was performed by two medically trained researchers (IZ and FST) independently. In case of disagreement consensus was sought via discussion, and in case of remaining disagreement, a third researcher arbitrated (SMS). The same approach was applied for the assessment of 'eligibility' of the key element for analysis in existing EHDs.

Table 1: Description of the key element categories based on objective and target group

Category	Description
Knowledge change	
Targeted at patients Targeted at HCPs	Information provision to increase the patients' or HCPs understanding and awareness of the risk associated with the drug, e.g. mechanism of action, risk factors of the safety concern, signs and symptoms of ADRs, risk frequency.
Behavioural change	
Targeted at patients	
Recommended actions to be followed during treatment use	Recommended actions or behaviour to be followed or avoided by the patient concerning treatment use, e.g. self-injection instructions, avoidance of grapefruit juice due to interaction risk, not giving the drug to another person.
Recommended actions to early detect or treat/ resolve ADRs	Recommended actions to be taken by the patient when an ADR or symptoms of an ADR occurs, e.g. contact your doctor.
Targeted at HCPs	
Recommended actions regarding drug prescription	Guidance on contra-indications, use of co-medication, dosage and duration of use, eligibility of the patients to receive the treatment.
Recommended actions regarding the drug administration process	Recommendations regarding drug reconstitution, administration and dispensing, e.g. prescription for qualified HCP or centres only, HCP should monitor the patient (or specific patient groups) directly after receiving the medication for a pre-specified period.
Recommended actions to perform clinical examinations and laboratory tests	The HCP should • perform pre-prescription assessments to exclude inappropriate use, i.e. pregnancy test, tuberculosis test. • examine the patient on a frequent basis to early detect ADRs.
Recommended actions to treat/resolve ADRs	Recommended actions to be taken on the management of the risks when an ADR occurs, e.g. discontinue treatment, lower the dosage, change medication, contact prescriber or specialist.
Other	
Pharmacovigilance instructions	Instructions regarding spontaneous reporting or other requirements to facilitate the collection of post-marketing safety data.
Not elsewhere classified	Recommendations regarding the facilities for identification and traceability of a medicinal product; the need for post-marketing and compliance assessment; differences in packing.

ADR=adverse drug reaction; HCP=healthcare professional

Key elements eligible for analysis in existing EHDs

In this study, EHDs refer to already existing computerised data sources containing routinely collected medical information from actual care and which are commonly used for pharmacoepidemiology and pharmacovigilance research.[8] There is wide variation between EHDs. To obtain characteristics of these type of databases, we explored the database registry of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), a collaborative scientific network in the fields of pharmacoepidemiology and pharmacovigilance.[7] EHDs included in this registry mainly are administrative (claims) databases, routine primary care databases, pharmacy dispensing databases and some contain also hospital data e.g. Danish Medical Registries, GPRD, THIN, HealthSearch, IMS Lifelink Health Plan US, IMS Lifelink EMR FR, IPCI.[11] In addition to the ENCePP database registry (www.encepp.eu/encepp/resourcesDatabase.jsp),[11] we explored a relevant overview of databases from the book Pharmacoepidemiolgy[12] to identify the type of information that can be retrieved from

existing EHDs. The information considered retrievable from existing EHDs in our study include: patient demographics, information regarding drug prescription/dispensing, medical events which can include adverse events, symptoms/signs, diagnosis in primary care, specialist diagnosis, hospital discharge diagnosis, laboratory values, death, clinical procedures, overdoses and teratogenic events. This information was the basis for the assessment whether the key element was eligible for analysis in EHDs. The researchers classified independently each key element as 'possibly eligible for analysis in EHDs', 'not eligible for analysis in EHDs unless more clearly defined', 'not eligible for analysis in EHDs' or 'not eligible for analysis at all' (Table 2).

Table 2: Description of the classes of 'eligibility for analysis in EHDs'

Possibly eligible for analysis in EHDs*	Not eligible for analysis in EHDs unless more clearly defined *	Not eligible for analysis in EHDs *	Not eligible for analysis at all
Data that reflects the desired effect of the key element (recommended actions resulting from the key element) is considered retrievable from EHDs. †	The key element was considered vague or ambiguously formulated and therefore the objective was not clear. If the key element would have been more clearly formulated, the data that reflects the desired effect of the key element (recommended actions resulting from the key element) is expected to be retrievable from EHDs. †	Data that reflects the desired effect of the key elements could not be retrieved from EHDs. Prospective data collection via survey (questionnaire or interview), patient chart review or any other method to collect information is needed for analysis.	The objective to minimise drug related risks is unclear or not applicable. Sine no effect with regard to a minimised risk could be achieved, these key elements were considered not eligible for analysis at all.

**EHDs=electronic healthcare databases. These include databases of routinely collected medical information that are commonly used in pharmacoepidemiolic and pharmacovigilance research and contain data on drug prescription, diagnosis and events.*
†The key elements are also eligible for analysis with newly collected data.

Data analysis

Descriptive statistics were used to describe the key elements and the possibility to analyse the key elements in existing EHDs.

RESULTS

By 1st April 2011, for 11 of the 227 active substances authorised before 2005 and 57 of the 199 authorised after the requirement on EU-RMP came into force in 2005 had aRMMs. The 68 active substances with aRMMs included in our study are presented in Appendix I. In total, 801 key elements were identified for these active substances. Table 3 shows that the median of the number of key elements per active substance was 9.5 (ranging from 1 to 68).

Table 3: Number of key elements per active substance

	Total (%)	Median number of key elements (range)	Active substances with at least one key element of that category
Total	801 (100)	9.5 (1-68)	68
Categorised key elements			
Knowledge change	287 (36)	3 (0-23)	59
Behavioural change	459 (57)	4 (0-42)	61
Others	55 (7)	0 (0-5)	25
Eligible for analysis			
Possibly eligible for analysis in EHDs	175(22)	2 (0-13)	49
Not eligible for analysis in EHDs unless more clearly defined	87 (11)	1 (0-5)	40
Not eligible for analysis in EHDs	521 (65)	5 (0-59)	63
Not eligible for analysis at all	18(2)	0 (0-3)	13

EHD=electronic healthcare database

The identified key elements are described in Tables 3 and 4. Overall, 36% of the key elements aimed knowledge changes and 57% aimed behavioural changes. 66% of the key elements were targeted to HCPs of which the majority (64%; 337 of the 529) aimed behavioural changes of this target group. These key elements were most frequently classified as 'recommended actions regarding drug prescription' (n=136) followed by 'recommended actions regarding the drug administration process' (n=94). 56% of the key elements targeted at patients (122 of the 217) aimed a behavioural change, which mainly concerned 'recommended actions to be followed during treatment use' (n=112). Per active substance the median number of key elements that aimed a knowledge change and behavioural change was 3 (range 0 - 23) and 4 (range 0 - 42), respectively.

The researchers assessed 22% of all key elements possibly eligible for analysis in EHDs based on the data that was considered retrievable from existing EHDs. None of these key element aimed a knowledge change. 37% of key elements that aimed a behavioural change (172 of the 459) was classified possibly eligible for analysis in EHDs of which the majority was targeted to HCPs (98%; 168 of the 172). These key element were most frequently classified as 'recommended actions regarding drug prescription' (n=88) or 'recommended actions to perform clinical examinations and laboratory tests' (n=58). Only 3% of the key elements classified as 'recommended actions regarding drug administration process' (3 of the 94) was assessed possibly eligible for analysis in EHDs.

16% of the key elements aimed at behavioural changes (72 of the 459) were assessed not eligible for analysis in EHDs unless more clearly defined. These key elements were distributed over 40 active substances and all targeted at HCPs. The majority was categorised as 'recommended actions regarding drug prescription' (67%; 48 of the 72), which correspond to 35% of the key elements in this category (48 of the 136). The majority of the key elements assessed not eligible for analysis at all (15 of the 18) concerned pharmacovigilance instructions, i.e. regarding the need to report adverse events.

Overall, 49 active substances (72%) had at least one key element (median of 3 key elements, ranging between 1 to 13) that was assessed possibly eligible for analysis in EHDs. Most frequently, this concerned a key element categorised as 'recommended action regarding drug prescription' (38 active substances) and for 28 active substances a key element categorised as 'recommended action to perform clinical examinations and laboratory tests'.

Table 4: Categorised key elements of the active substances with aRMMs licensed at 1 April 2011

Category	Number of key elements					Number of active substances	
	Total (%) *	Possibly eligible for analysis in EHDs (%)†	Not eligible for analysis in EHDs unless more clearly defined (%)†	Not eligible for analysis in EHDs (%)†	Not eligible for analysis at all (%)†	Total (%) *	With key elements eligible for analysis in EHDs §
Total	801 (100)	175 (22)	87 (11)	521 (65)	18 (2)	68	49
Knowledge change							
Targeted to patients	95 (12)	0 (0)	0 (0)	95 (100)	0 (0)	31	0
Targeted to HCPs	192 (24)	0 (0)	15 (8)	177 (92)	0 (0)	56	0
Behavioural change							
Targeted to patients							
Recommended actions to be followed during treatment use	112 (14)	4 (4)	0 (0)	108 (96)	0 (0)	23	3
Recommended actions to early detect or treat/ resolve ADRs	10 (1)	0 (0)	0 (0)	10 (100)	0 (0)	8	0
Targeted to HCPs							
Recommended actions regarding drug prescription	136 (17)	88 (65)	48 (35)	0 (0)	0 (0)	46	38
Recommended actions regarding the drug administration process	94 (12)	3 (3)	6 (6)	85 (90)	0 (0)	38	3
Recommended actions to perform clinical examinations and laboratory tests	73 (9)	58 (80)	8 (11)	7 (10)	0 (0)	34	28
Recommended actions to treat/resolve ADRs	34 (4)	19 (56)	10 (29)	5 (15)	0 (0)	19	11
Other							
PhV instructions	44 (5)	3 (7)	0 (0)	26 (59)	15 (34)	22	3
Not elsewhere classified	11 (1)	0 (0)	0 (0)	8 (73)	3 (27)	9	0

ADR=adverse drug reaction; EHD=electronic healthcare database; HCP=healthcare professional; PhV=pharmacovigilance
**Colum percentage*
†Row percentage of the total number of key elements of that category
§ One active substance can have multiple key elements concerning different categories

DISCUSSION

This study provides a first review on the eligibility of aRMMs for analysis in existing EHDs. Currently, 22% of the aRMM key elements are considered suitable for assessment in EHDs, based on the information we considered retrievable from these data sources. These mainly concerned key elements aimed at behavioural changes of HCPs, e.g. recommendations regarding the dose, concomitant medications or to perform a laboratory test.

Overall, only 50% of the key elements aimed at behavioural change of HCPs were assessed eligible for analysis in EHDs. For those key elements that were not considered eligible for analysis in EHDs, either the data necessary to measure the desired effects were not recorded routinely in these systems or the key elements per se were not clear and do therefore not allow monitoring. Still 21% of the key elements aimed at behavioural changes of HCPs were assessed not eligible for analysis in EHDs due to ambiguous formulated key elements, e.g. use the drug with caution; carefully select patients. These key elements should be reformulated into clear recommended actions. This could improve the adherence to the aRMMs and facilitate rapid assessment of aRMM effectiveness. It is in the interest of individual patients and public health that industry and regulatory authorities work with carefully formulated aRMMs resulting in clear objectives that optimise the benefit-risk balance of a drug.

Key elements that aimed behavioural changes in patients (e.g. recommendations for patients on how to take their medication or a warnings to avoid exposure to sunlight) are difficult to monitor in existing EHDs, since it is unlikely this information is routinely collected and captured by EHDs. The same holds for key elements aimed at knowledge change which covered a large proportion of all key elements, e.g. information on the most serious adverse reactions of the drug; information on the medical implications of a drug-drug interaction. If these recommendations and knowledge are deemed essential for maintaining a positive benefit-risk balance, the challenge is how to analyse its effectiveness in a swift and proper way using prospective data collection. aRMMs aiming a knowledge change may contribute considerably to the aRMM effectiveness and can therefore not be disregarded. Risk awareness is an essential aspect to obtain behavioural changes.[13] In addition, education on early recognition of signs and symptoms of ADRs can improve the patient's outcome, relevant for individual patients as well as for public health.[14]

Data collection

As shown in this study, approaches that go beyond the use of EHDs are needed to allow assessment of knowledge and behavioural changes. It remains however a challenge to perform these aRMM analyses timely and in an appropriate way. Alternative strategies to prospectively collect new information can include surveys (questionnaire or interviews) or review of case reports or patient's charts.[15-17] Prospective data collection via surveys can be time consuming and delay the assessment whereas insufficient aRMMs need to be identified in an early stage to enable prompt improvement. Furthermore, surveys can yield non-response bias and sampling error that may prevent drawing valid conclusions from the assessment of aRMM's effectiveness.[18, 19] However, also the number of subjects using drugs with aRMMs available in EHDs can be limited, particularly in outpatient setting (i.e. general practice databases) since drugs with aRMMs are often used for treating serious disease in hospital. The type of data used for the evaluation of aRMMs and the possible impact on the methodology, validity of the data, time planning, possible outcome measures or other potential biases should be well considered by researchers, regulators and MAHs.

Strengths and limitations of the study

A formal categorisation for aRMM key elements does not (yet) exist. Because of the heterogeneity of the data, we classified the key elements based on objective (knowledge and behavioural change) and target group in ten categories. This categorisation was necessary to adequately describe the key elements in our study, but may need further improvement. However, using smaller categories result in many key elements that can be classified in several categories which would be complicated and inaccurate. It will also increase the chance of misclassified key elements.

Existing EHDs can vary substantially and we did not formally review particular EHDs. Instead, we used the knowledge available regarding such data sources and obtained characteristics of EHDs commonly used within pharmacoepidemiology and pharmacovigilance research from ENCePP. Our aim was not to draw conclusions regarding specific databases, while providing information about the eligibility to analyse the effectiveness of aRMM in these resources. We assessed whether in general an aRMM might be suitable for analysis in existing EHDs. The feasibility of particular databases need to be verified separately.

To our knowledge, this is the first study that reviewed whether the approved aRMMs in the EU are eligible for analysis specially in existing EHDs. The results of this study can be used to improve aRMMs, and facilitate monitoring of effectiveness which is mandatory since the new EU pharmacovigilance legislation. To facilitate assessment of aRMM's effectiveness, besides the need for well-defined aRMMs with clear objectives, there is a need for pre-defined indicators of success to be agreed in a study protocol. Without pre-defined objectives the assessment of the aRMMs and its effect on clinical practice and consequently the benefit-risk balance of a drug may still be open for discussion. Although some guidance is available,[1, 10, 20] there is a clear need for further development of evaluation methodologies and interpretation of the outcomes with regard to the benefit-risk balance of the drug.

Conclusions

Using readily available data from existing EHDs provide an efficient way to allow rapid and timely assessment, which is necessary to modify aRMMs and improve implementation in early stages if warranted. However, the results of the study show that only a limited proportion of the key elements of aRMMs is considered eligible for analysis in existing EHDs as these data sources cannot capture all the required data. Due to difference between existing EHDs, not necessarily all available EHDs will be appropriate to monitor effectiveness for every drug or aRMM. Based on these findings, industry and regulatory authorities should agree on well-defined aRMM key elements leading to unambiguous actions of the target group. This could improve adherence to aRMMs and facilitate the assessment of effectiveness of aRMMs which is a new legal obligation for MAHs and regulatory authorities.

Appendix I: Active substances with aRMMs included in the study and their key elements

Active substance	Number of key elements	Active substance	Number of key elements
5-aminolevulinic acid hydrochloride	15	lasofoxifene	7
abatacept	1	leflunomide	6
adalimumab	5	lenalidomide	52
agomelatine	7	mecasermin	16
alemtuzumab	7	methoxy polyethylene glycol-epoetin beta	6
ambrisentan	47	micafungin	9
anidulafungin	7	moroctocog alfa	16
besilesomab	1	natalizumab	13
bosentan	23	nilotinib	11
caffeine	12	nonacog alfa	10
canakinumab	10	olanzapine	15
capsaicin	6	pandemic influenza vaccine (Focetria©)	5
certolizumab pegol	5	pandemic influenza vaccine (H1N1)	5
characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins. (ChondroCelect©)	11	(Humenza©) pandemic influenza vaccine (H5N1) (Celvapan©)	5
collagenase clostridium histolyticum	7	pandemic influenza vaccine (H5N1) (Pandemrix©)	5
conestat alfa	21	pegaptanib	13
deferasirox	18	pirfenidone	8
degarelix	4	pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	2
dexamethasone	10	porfimer	27
dronedarone	12	prasugrel	5
eculizumab	4	ranibizumab	10
efavirenz/emtricitabine/tenofovir disoproxil	1	ranolazine	14
eltrombopag	27	retigabine	4
epoetin alpha	5	rilonacept	11
eptacog alfa (activated)	9	roflumilast	17
eptotermin alfa	10	romiplostim	12
fentanyl (buccal tablets)	17	sevelamer	3
fentanyl (nasal spray)	19	sildenafil	3
fingolimod	17	silodosin	5
gadoversetamide	3	thalidomide	68
golimumab	5	tocilizumab	13
hydroxycarbamide	14	ustekinumab	9
indacaterol	3	vernakalant	15
infliximab	6	zoledronic acid	12

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4

POST-APPROVAL EVALUATION OF EFFECTIVENESS OF RISK MINIMISATION:

METHODS, CHALLENGES AND INTERPRETATION

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ABSTRACT

Evaluation of the effectiveness of drug risk minimisation measures is mandatory for both risk evaluation and mitigation strategies (REMS) in the United States and risk management plans in the European Union (EU-RMPs). Such evaluations aim to assess the impact of risk minimisation measures on the knowledge, attitudes or behaviours of healthcare professionals or patients, the incidence of safety concerns, and their impact on the overall benefit-risk balance. Although many effectiveness evaluation models and methods are available, regulatory guidance and policy are still evolving. This paper considers evaluation strategies, challenges in evaluating risk minimisation post-authorisation, possible outcome measures and their interpretation, and potential emerging regulatory policy issues. Particular challenges include appropriate data collection, perceived and real burdens of performing evaluation on clinical practice, lack of comparators and benchmarking, and uncertainty about the best outcome measures.

INTRODUCTION

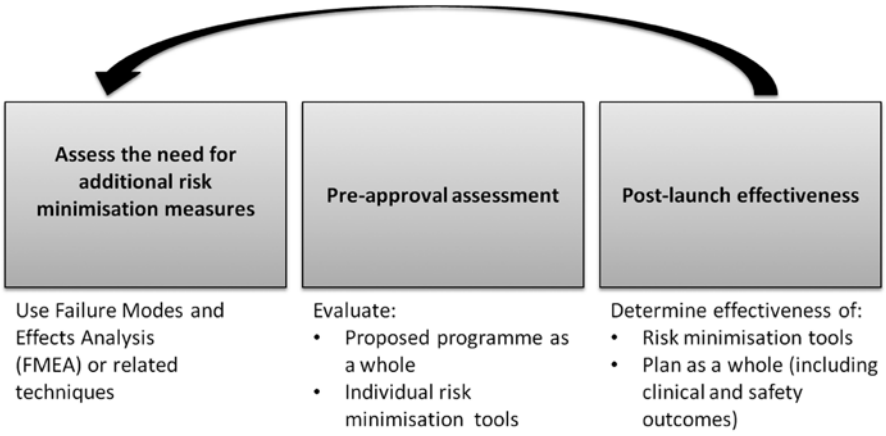
For some drugs with serious risks it may be necessary to improve the benefit-risk balance with measures extending beyond the routinely required summary of product characteristics (SmPC), package leaflet, packaging labelling, pack size and design, and legal status of a drug.[1] In the European Union (EU), such extra activities are referred to as additional risk minimisation measures (aRMMs).

Examples of aRMMs include educational programmes for healthcare professionals (HCPs) and patients, and required interventions such as pre-prescription screening of patients to ensure the appropriate patient population.[2] The measures are often implemented through use of appropriately selected tools, such as a prescriber brochure and patient card. In the EU, when an aRMM is necessary, this is set out in the risk minimisation section of the risk management plan (RMP), a mandatory part of all new marketing applications.[3] The RMP considers the important identified and potential safety concerns of the drug and missing information within the safety specification, the planned pharmacovigilance activities to monitor and further characterise these safety concerns during the post-marketing period (including post-authorisation safety studies), and risk minimisation measures (RMMs), both routine and additional, that aim to prevent and mitigate the safety concerns in clinical practice.[1] In the United States (US), the Food and Drug Administration (FDA) can require a risk evaluation and mitigation strategy (REMS) for a medicinal product, which can be a compulsory element of usage of the drug.[4] Although the specific legislation differs between EU and the US, in both jurisdictions these additional measures are interventions that aim to minimise the occurrence and/or impact of adverse drug reactions (ADRs).

The risk management approach, including the use of RMMs, is evolving,[5] and new standards are required under the EU pharmacovigilance legislation that came into effect in 2012.[1, 6, 7] The need for aRMMs or a REMS is evaluated during the registration process of a drug and also on a continuous basis during the lifecycle of the drug (Figure 1). The number of products with aRMMs has grown. The proportion of centrally approved active substances with aRMMs in the EU was 5% among products authorised before the RMP became mandatory in 2005; and 29% among products approved afterwards.[2] As a result, the need for adequate evaluation has also increased.

Measuring effectiveness of the RMMs and REMS post-marketing is an important part of the continuous re-evaluation of the benefit-risk balance of a drug. This also includes an assessment of whether the existing RMMs are sufficient and enables modification of the initial measures to improve the risk minimisation strategy if warranted. A feedback loop to detect potential issues with the adopted RMMs, so that corrective actions can be implemented promptly, is a key component of the overall approach. With the recent EU pharmacovigilance legislation, monitoring the effectiveness of the aRMMs has become mandatory for both marketing authorisation holders (MAHs) and regulatory authorities.[6]

Figure 1: Evaluation of risk minimisation at different lifecycle stages



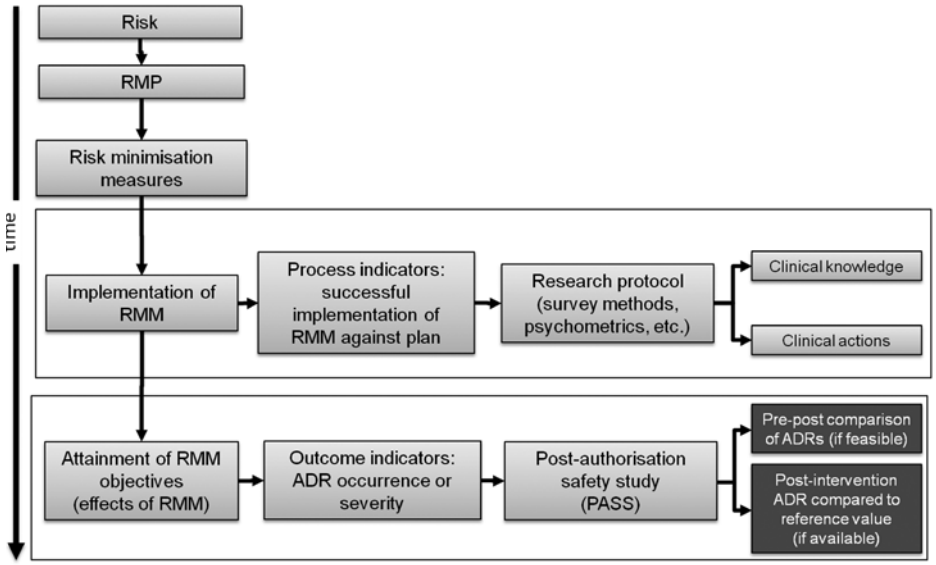
In the US, a REMS assessment plan needs to be approved in advance of REMS implementation. The REMS effectiveness analysis is normally needed at 18 months, 3 years and 7 years after REMS approval.[4] The REMS assessments should include an evaluation of the extent to which each of the REMS elements is meeting the goals and objectives of the REMS, and whether or not the goals, objectives, or REMS elements should be modified. Other regions are developing their own RMP requirements. Many are based closely on the EU-RMP template (such as Brazil), some have a country-specific addendum (such as Australia), whilst others, including Japan, have implemented their own template. However, it is likely that all will require some form of post-launch evaluation of any aRMMs, so the principles discussed in this paper are relevant for their potential impact on global regulatory policies.

Currently, there is limited knowledge on the approaches for evaluating tools, and the determinants of success of RMMs. In this paper, the evaluation strategies and the challenges involved in evaluating RMMs during the post-marketing phase are discussed. Potential outcome measures and their interpretation are also considered.

MODELS OF EVALUATION OF EFFECTIVENESS

Prieto et al.[8] described a model assessing RMMs and their implementation (process indicators), including measurement of tool delivery and acquired clinical knowledge, as well as the resulting clinical behaviours. Effectiveness of the risk minimisation strategy as a whole can be evaluated by demonstrating a reduction in the occurrence or severity of ADRs (Figure 2). A key goal for some programmes may be appropriate patient selection to ensure maximal benefit-risk balance. Proper patient selection may exclude high-risk patients from treatment or could optimise outcomes by maximising benefit even though the frequency and severity of ADRs may not change. Prieto's model usefully differentiates between process indicators and final outcome indicators, providing a basic hierarchy of evidence for RMM evaluation. However, both this model and the good pharmacovigilance practices (GVP) Module XVI on the evaluation of risk minimisation measures remain relatively non-specific regarding detailed methodology for evaluating the risk minimisation plan as a whole; other than suggesting the use of epidemiological outcomes studies.[1, 7]

Figure 2: Evaluation of the effectiveness of risk minimisation plans by a dual evidence approach – the implementation process and the outcomes (adapted from Prieto et al.[8]

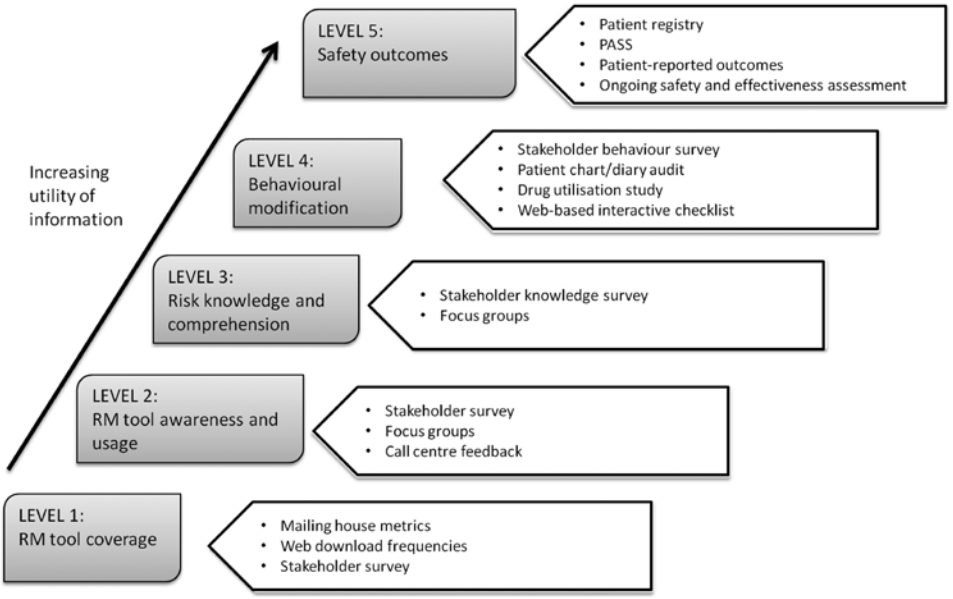


ADR=adverse drug reaction; RMM=risk minimisatoin measures; RMP=risk management plan

A 5-level model[9] (Figure 3) with different evaluation levels, resulting in increasing utility of information, may be used to determine RMM effectiveness. The evaluation levels range from: level 1 (risk minimisation tool coverage) addressing the distribution of the risk minimisation tools, to level 5 (safety outcomes), covering linkage of risk minimisation tool usage to safety outcomes, i.e., occurrence of ADRs. Behavioural (level 4) and safety outcomes (level 5) data may be harder to obtain but generally have higher value than information on tool coverage (level 1), awareness and usage (level 2) and knowledge (level 3) metrics. The effectiveness of individual tools can be measured at all levels, whereas the success of the overall programme in meeting goals and objectives can be evaluated at levels 3 to 5. This 5-level model adds a detailed hierarchy of evidence into the evaluation of tools, and attempts to link the evaluation of individual tools and the risk minimisation plan as a whole into a single continuum.

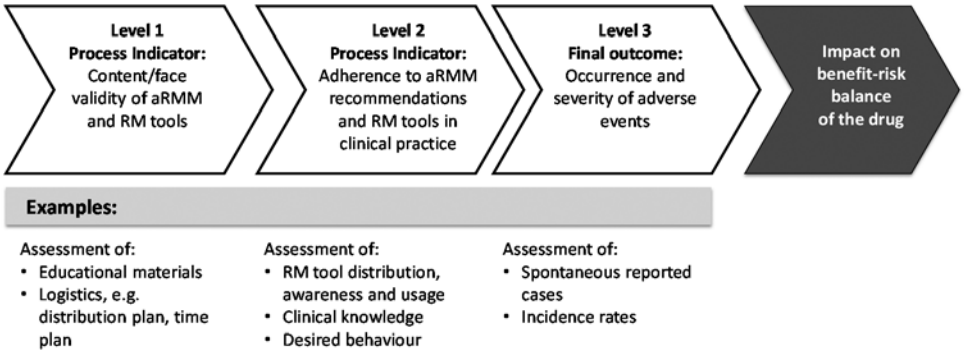
A complementary model[10] (Figure 4) evaluates effectiveness at various intervals. In this model, the complete RMM strategy and risk minimisation tool content and face validity can be assessed in level 1 (pre-approval phase). Assessment of the implementation of the risk minimisation tools includes use of the tools and the acquired clinical knowledge and behaviour (level 2). The overall effectiveness of the RMM and the impact on the occurrence or severity of the safety concern is assessed in level 3. The second and third levels provide complementary information relevant for the assessment of the RMM's impact on the benefit-risk balance of the drug. This latter model makes the iterative elements of evaluation, correction and re-audit integral to the overall chronological process. These three models should prove useful for communicating the concept of assessing both implementation and outcomes, and aiding more detailed planning of components in the evaluation of effectiveness post-marketing.

Figure 3: A 5-level framework covers both individual risk minimisation tools and programme evaluation, and focuses on the quality of evidence



PASS=post authorisation safety study; RM=risk minimisation

Figure 4: Evaluation steps increase in utility of information with time after implementation[10]



aRMM=additional risk minimisation measure; RM=risk minimisation

SHORTCOMINGS OF CURRENT RISK MINIMISATION EVALUATION APPROACHES

Regardless of the model, a number of challenges emerge when considering effectiveness evaluation systems in general.

Appropriate data collection

Appropriate data collection is important to adequately assess the RMMs and many data sources can be used. Some examples of potential suitable metrics and their interpretation are shown in Table 1 for each level of the 5-step model. Information on patients' or HCPs' knowledge, behaviour and drug use can be prospectively collected via surveys. With this type of data collection, specific and detailed information from the target group can be collected. However, issues with recruiting participants; and small or unrepresentative sample sizes may occur which make it difficult to draw robust conclusions.[11]

Table 1: Possible risk minimisation tool evaluation metrics and suggested interpretations based on the 5-level model (see Figure 3)

Evaluation level	Example metrics and data to be collected	Interpretation
Level 1: Risk minimisation tool coverage	Tool distribution over time (in total and by category, such as country or type of HCP) Download frequency of electronic tools	Increase or decline in tool use and geographic coverage over time
Level 2: Risk minimisation tool awareness and usage	Rate of tool use over time (including by country, region, or type of HCP) Which fields within a tool are completed and the time taken	Gaps or bottlenecks in access and active tool use
Level 3: Risk knowledge and comprehension	How frequently specific information about drug-related risks is accessed for an electronic tool Results from knowledge surveys for both tool users and non-users	Whether the level of knowledge about key risks and their mitigation is sufficient, or suggests modifications to tools are required Whether knowledge is due to the tools or gained from other sources
Level 4: Behavioural modification	Extent of deviations from ideal behaviour (e.g. off-label prescribing) Frequency of linked risk minimisation actions (e.g. HCP providing patient with educational information)	Appropriateness of actions by HCPs and patients, consistent with the product information and best practice guidance where available (e.g. for patient selection and providing the appropriate information to the right patient)
Level 5: (Correlation with) Safety outcomes	Relevant ADR frequencies and severities	Comparing ADR rates and/or severities from suitable sources against appropriate reference values

ADR=Adverse drug reaction; HCP=Healthcare professional

An independent study of REMS assessments submitted by MAHs and reviewed by the FDA in the period 2008 to 2011, highlighted issues with submission on time, completeness and meeting their stated goals. The issues identified included difficulties with data collection (predominantly survey-based methods were used) and sample sizes that were too small for enabling conclusions to be drawn. Almost half of the REMS assessments reviewed did not include all the information requested in FDA assessment plans. Based on these results, the FDA was recommended to identify and implement reliable methods for assessing the effectiveness of REMS, decrease its reliance on survey data in REMS assessments and work with MAHs and HCPs to develop more accurate evaluation methods.[12]

Other known limitations for surveys include sample populations that do not reflect the demographics of the target population, bias caused by convenience samples ('lower-risk' patients and HCPs are often more likely to take part in such surveys[13, 14]) and a lack of objective standards to measure knowledge of risks. Furthermore, knowledge and behaviour surveys are usually based on a subject's recall of events or expectations, rather than direct measurement of how risk education affects behaviour, meaning surveys may fail to reflect real tool use and utility for all intended users. Response rates to surveys are often low, indicating that they may represent a burden on clinical practice.[15]

Evaluations of aRMMs or REMS effectiveness that allow assessment of safety outcomes often rely on integration with data sourced from electronic healthcare records, or from disease or drug registries,[16, 17] as electronic healthcare databases include information on drug prescription (which reflects the HCP's behaviour) and patient safety outcomes. These data sources are often used within pharmacoepidemiology and pharmacovigilance research and provide opportunities to study effectiveness of RMMs. Using routinely collected data reflecting actual care is efficient, and timely feedback on the RMMs may be provided. However, electronic healthcare databases may not capture sufficient and relevant data[10] and only cover some drugs.[18] Examples of electronic healthcare databases are the administrative (claims) databases, routine primary care databases, pharmacy dispensing databases, hospital databases and disease/drug registries.[19, 20] Several claims databases (e.g., Premier in the US) and prescription databases, such as the Nordic prescriber databases and Clinical Practice Research Datalink (CPRD), can give valuable information on drug utilisation. Studies can examine the extent of off-label use, indication, dosage and prescriber characteristics, offering useful indirect information on safety outcomes that can be correlated with behaviours. However, although HCP behaviour on drug prescribing and patient follow-up information in the form of coded events is available, knowledge cannot be measured from these data sources.

Spontaneous reporting systems are also possible data sources as these include case reports of patients that developed adverse events. These systems, however, suffer from biases such as under-reporting and lack of a suitable overall denominator (i.e., total exposure to the drug, number of patients exposed or number of drug doses administered), which inevitably hampers interpretation of results. The use of spontaneous reports may therefore not be suitable or sufficient.

Another issue is the timing of effectiveness evaluation. The interval between tool deployment, data collection, interpretation and actioning changes can often be a number of years, whereas ideally, efficient and timely evaluation is needed to allow early closure of the audit loop and timely aRMM amendment if necessary. It takes time for a newly-launched drug to sufficiently penetrate the market and often certain sample sizes are necessary to be able to observe desired effects and draw conclusions on the study outcomes. Therefore, the timing of assessment should be appropriate for the intervention, and the expectations of all stakeholders, including regulators, should be realistic. REMS have a mandated timeline for assessments which may not be an appropriate fit for every REMS.

Overall, strengths and limitations of the type of data collection should be carefully considered on a case-by-case basis depending on the RMMs, the safety concerns and drug involved.

Lack of comparators

Drugs with RMMs that are required at the time of initial marketing authorisation do not have defined, unbiased comparator groups of tool non-users for post-launch RMM evaluation. Post-hoc analysis may be used, where risk minimisation tool users are compared with non-users, although in practice it may be difficult to distinguish them. Furthermore, there may be other confounding factors, such as a propensity to riskier clinical practice by 'non-users' that contributes to an increased risk of occurrence of a particular safety concern. This makes any observed difference difficult to attribute to any positive effects of the tools themselves.

It would also not be ethical in the post-approval setting to have a control group where RMMs, that contribute to the favourable benefit-risk balance of the drug, were not available. However, when the value of the risk minimisation is unclear, a potential approach could be a phased implementation of aRMMs that initially includes a comparator population that does not use the aRMMs. Such an approach has been utilised for modifying the risk minimisation of an already-launched antifungal product, with the management of unresolved hepatotoxicity safety issues involving a modified aRMM approach piloted in two EU countries, prior to interim evaluation and subsequent rollout in the rest of the EU.[21]

An alternative solution would be to test the proposed risk minimisation measure in a proportion of the phase III study population. This allows some valuable comparative information to be gained, albeit not in a real-world setting. It may also be possible to compare different drugs, with and without aRMMs, or compare the safety outcomes for the drug with a reference value for the target or general population.[22] Nevertheless, all comparisons will have their limitations and the most appropriate solution should be selected on a case-by-case basis, and will be dependent on the data available.

Lack of meaningful outcomes

RMMs aim to minimise the inherent risks of drug treatments, thus optimising the benefit-risk balance of the drug. Ideally, successful implementation should lead to a reduced ADR rate and/or severity, by increasing the patients' and HCPs' knowledge and adapting their behaviour (e.g., appropriate patient selection), as shown in Figure 2. Since the aRMMs are developed for each drug product independently, a 'gold standard' set of standard outcome measures cannot currently be defined and only the broad outcomes can be outlined.

For example, in drugs with the risk of teratogenicity, a meaningful outcome is prevention of pregnancy or no fetal exposure to the drug in question. The aim is to guide desired behaviours (e.g., use of contraceptives and HCPs providing appropriate advice to patients) to meet this goal.[23] However, even with drugs such as isotretinoin, where strict RMMs have been implemented in the form of a pregnancy prevention programme, pregnancies still occur. The real outcome of interest might be minimisation of infants with congenital malformations by preventing pregnancies.[24, 25] In the case of pregnancies occurring, the issue of determining an acceptable threshold based on the benefit-risk profile of the drug still arises; that is, evidence of successful effectiveness of an RMM relies on a stated goal for defining success.[26]

Most evaluations have so far concentrated on measures of process, such as tool distribution and utilisation results, rather than clinical outcomes, such as reducing or eliminating ADRs, or fewer

patients with absolute or relative contraindications.[26] The three models discussed earlier highlight the need to also evaluate the latter.

Linking risk management activities to meaningful changes in safety outcomes remains a challenge, as demonstrated by the FDA's recent exercise to address prescription opioid abuse and over-prescribing,[27] which mirrors the experience in other markets. Although evaluation of effectiveness was being performed, the data collected failed to either support the goal of improving RMMs, or providing evidence to enable future 'de-commissioning' of RMMs that have outlived their original purpose.

Uncertainty about interpretation of evaluation metrics

It is rare to be able to directly associate a reduction in ADRs with specific RMMs. Often, only cross-sectional data on safety outcomes are available that are not directly linked to data on the patients' usage/non-usage of tools. Baseline data on knowledge and behaviour are also frequently not available.

Spontaneous reporting rates of ADRs have too many biases, such as under-reporting, to enable a change in the frequency of ADR reports to be directly attributed to a risk minimisation intervention. This is particularly the case in the period shortly after the aRMM has been introduced or when there has been public communication about a serious event. The outcome may be an apparent rise in spontaneously reported ADRs, due to better prescriber and patient awareness of a risk increasing the reporting rate rather than an increase in the actual ADR rate.

The impact of RMMs on drug use is difficult to predict. Reber et al.[28] examined changes in use for 58 new drugs following direct healthcare professional communications (DHPCs) – colloquially known as 'Dear Doctor letters'. The results showed that DHPCs have a complex effect in changing clinical prescription behaviour. In about half the evaluated cases, DHPCs lowered overall drug use in the short term, and for around a third of the drugs long-term use was reduced.

Examination of prescribing outcomes linked to the patient's condition can identify patients in risk groups who may be receiving the drug inappropriately (i.e., not in line with the risk minimisation recommendations). HCPs may decide to prescribe a drug not in accordance with the recommended RMMs based on valid clinical reasons for individual patients; whereas the aRMMs and REMS aim to improve the benefit-risk of a drug at a patient population level. Whilst this is acceptable, it means that 100 percent adherence to risk minimisation recommendations is not feasible in clinical practice. However, if the frequency or severity of reported ADRs remains high and the benefit-risk balance of the drug therefore remains uncertain, appropriate regulatory action should be taken. This may include modification of the risk minimisation strategies.

Lack of benchmarking

It is difficult to predict what acceptable levels of distribution, tool uptake and impact on knowledge, behaviours and attitudes, constitute success. A first round of evaluation, following market authorisation, provides a benchmark, against which future evaluations may be compared. As the number of drugs with aRMMs grows, and experience with evaluating these measures evolves, acceptable outcome measures will be developed. Such benchmarking will allow newly-introduced aRMMs to be compared against these first-round evaluation measures. However, in order to be meaningful, benchmarking will need to cover different patient groups, specialist versus generalist prescribers, geography and therapeutic area, as these and similar factors may alter risk minimisation tool uptake. Further research

is needed to understand the impact of these multiple factors on influencing the implementation of individual RMMs. Continued collaboration between industry and regulatory agencies will be necessary, to facilitate and agree suitable benchmarking metrics, and will also require an overt regulatory policy on greater transparency on publication of the results of effectiveness evaluation.

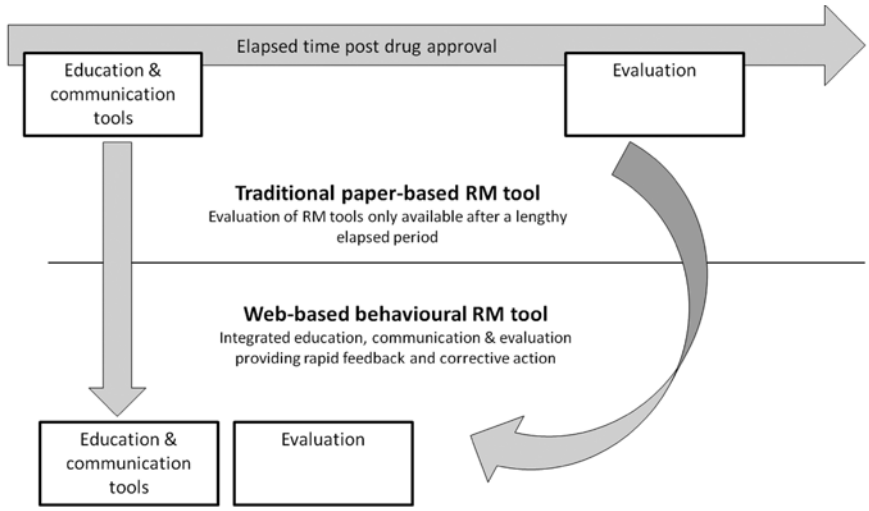
INNOVATIVE WEB-BASED TOOLS FACILITATE DATA COLLECTION

Many of the shortcomings of current evaluation methods could be addressed by implementation approaches that allow consistent, timely collection of evaluation data, relevant to the objectives of the specific RMMs deployed.

Web-based risk minimisation tools can facilitate data collection for the evaluation of the aRMMs. They can be combined with simultaneous collection of data reflecting actual behaviour of tool users, providing timely and ongoing evaluation (Figure 5).[29, 30] Internet facilities in healthcare centres are widely available globally. For example, in the EU an estimated 80 percent of hospitals have implemented electronic patient record systems, suggesting a potential to become paperless in future.[31] This supports an increase in both web-based risk minimisation tools and web-centric risk minimisation evaluation programmes.

Web-based tools can enhance HCP-to-patient communications (Pope Woodhead. User testing for new drug product X. 2013), for example, enabling HCPs to send automated reminder messages to patients. Furthermore, web-based tools can be used to confirm whether patient counselling was provided when the drug was prescribed, encourage ADR reporting and link tools to other post-launch data-gathering initiatives, including spontaneous reporting systems and registries. Routine collection of anonymised data from risk minimisation tool users, processed continuously in real time, permits rapid assessment of the effectiveness of the implementation and tools themselves, and provides a straightforward approach to periodic evaluation.[32] In the future, patient-reported outcomes of adverse events (PRO-AEs) may offer a useful and relevant approach for assessing the success of RMMs.[33, 34] However, a number of factors need to be considered when deploying web-based RMMs (for both HCPs and patients), for example, tool penetration and usability, how to achieve coverage where the internet is not available, and data protection issues (which may vary between countries). Hence, a web-based risk minimisation approach that incorporates evaluation requires careful design and supporting IT infrastructure, though over the lifetime of a product. Complexity can also arise in integrating data from multiple sources such as PROs, patient drug lists, health outcomes, provider education and assessment results. The numerous health records systems within the US and differences between EU member states provide further complexity.

Figure 5: Web-based behavioural risk minimisation tools can combine education, communication and real-time evaluation



RM=risk minimisation

POTENTIAL IMPACT ON REGULATORY POLICIES

From a regulatory policy perspective, aspects to consider include corrective actions, establishment of an agreed baseline, and potentially more combined/single RMPs for a product class to allow more impactful comparisons.

For effectiveness evaluation to be useful, an audit loop should be closed; i.e., corrective actions should be taken based on the collected results if necessary. Whilst appropriate actions may include modifying the aRMMs or individual risk minimisation tools, sometimes the MAH in conjunction with regulatory authorities might consider making the programme less onerous (particularly if it is clear that adequate risk minimisation is successfully occurring without the need for tool intervention; e.g., despite low tool usage).

Effective processes in risk management are essential, so steps should be incorporated to allow elimination of ineffective tools or programmes. Measures impose a considerable burden on clinicians, support staff and patients, and are often expensive to implement. Effectiveness depends on the quality of the tools and overall programme and both should be scrutinised, by establishing clear success criteria for each. Table 2 outlines proposed actions to improve effectiveness of both risk minimisation tools and the aRMMs overall for a product. The suggested action depends on the success of the deployment versus the effectiveness of risk minimisation as a whole. In this framework, deployment is defined by tool coverage and usage, measured by distribution/utilisation and tracking metrics (levels 1 and 2 of the 5-level model shown in Figure 3); and effectiveness of the risk minimisation is measured by knowledge, attitudes and behaviours and the safety outcomes themselves (levels 3, 4 and 5 of the 5-step model in Figure 3).

Table 2: Possible actions following risk minimisation effectiveness evaluation

	Effectiveness of risk minimisation	
Deployment of risk minimisation measures	*Low*	*High*
Low	1. Increase tool awareness via enhanced education and communication with HCPs 2. Targeted training to increase correct tool use[a] 3. Adapt tools to encourage greater utilisation[c] 4. Introduce stricter controls to drive tool use (e.g. compulsory rather than voluntary)[c] 5. Re-evaluate to ensure effectiveness	1. Consider whether risk minimisation measures can be scaled back[b] 2. If measures are modified, re-evaluate to ensure adequate risk minimisation is maintaine[d]
High	1. Redesign risk minimisation strategy and reconsider choice of risk minimisation tools[d] 2. Modify the content and format of tools, as appropriate 3. Re-evaluate to ensure effectiveness	1. Continue risk minimisation in current form 2. Further evaluation to ensure standards are maintained[e]

HCP=Healthcare professional
[a] *If utilisation of the distributed tools is low,[35] raise awareness or provide training as a first step[36, 37]*
[b] *Monitoring of tool effectiveness over time may indicate appropriate use of the drug, leading to the opportunity to reduce or remove aRMMs[38]*
[c] *Many programmes have experienced fewer than 20 percent of prescribers and patients using the tool(s)[39]*
[d] *Collaboration with stakeholders is important in the design of aRMMs.*
[e] *Over time, wider experience of aRMM evaluation may allow therapy- and user- specific acceptable ranges for tool usage to be established[22]*

Other issues that potentially impact regulatory policy will be a move towards transparency of the results of effectiveness evaluation and corrective actions taken. This will eventually allow prospective benchmarking and, potentially, the setting of target standards of deployment expected from MAHs at the time of approval if possible. Greater harmonisation between the aRMMs, perhaps with class-specific risk minimisation, would allow greater efficiency and less confusion for prescribers and patients, promoting greater engagement of the end-user with voluntary aRMMs.[40]

Regulators should ensure that the requirements for effectiveness evaluation of aRMMs with accepted methodologies are transparent.

CONCLUSIONS

Measuring the effectiveness of aRMMs and REMS is an important aspect of the benefit-risk evaluation of a drug. Limited detailed guidance is currently available on the evaluation of effectiveness of aRMMs, leading to a lack of consistency which is only partly addressed by the recent GVP guidance and the REMS guidance. Available models include assessment of effectiveness at different levels, with varying utility of information.

Specific challenges in evaluation include appropriate data collection, lack of comparators, uncertainty on the best outcome measures and lack of benchmarking or pre-defined aRMM objectives, which may be indicative of a weak underlying risk minimisation strategy. The difficulty of collecting adequate and timely data may be impeding evaluation of effectiveness of aRMMs. The result is that the reaction time to safety issues is slow, and revisions to implemented RMPs to address potential safety issues are protracted.

Optimal risk minimisation evaluation involves assessment of aRMM deployment and use, as well as the knowledge and behaviour of patients and HCPs, and the safety outcomes. Evaluation methods need to be tailored to specific safety concerns, the actual aRMMs deployed and the drug involved. Global regulatory policy must also embrace industry, patients and prescribers to pre-define comprehensive, but feasible, objectives and evaluation plans and iteratively close the audit loop in a timely way on any aRMMs.

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5

IMPACT OF RISK MINIMISATION MEASURES ON CITALOPRAM USE IN TWO EUROPEAN COUNTRIES

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ABSTRACT

Background In October 2011 risk minimisation measures in the form of dose restrictions were recommended to minimise the dose dependent risk of QT interval prolongation associated with citalopram. The maximum daily doses were reduced from 60 mg to 40 mg and in patients aged ≥ 65 from 40 mg to 20 mg. The objective of this study was to assess the impact of these recommendations on the use of citalopram in the Netherlands (NL) and the United Kingdom (UK).

Methods A retrospective population-based study was conducted within primary care databases in NL (IPCI: 1998 – 2012) and UK (THIN: 1996 – 2013). Monthly prevalence and incidence rates of citalopram were calculated (users/1,000 person years (PY)) and stratified by country, age group (<65; ≥ 65) and daily dose category ≤ 20 mg (low); >20 to ≤ 40 mg (moderate); > 40 mg (high). Interrupted time-series analysis using an ARIMA (autoregressive integrated moving average) model was performed to assess the effect of the dose restrictions on the use of citalopram.

Results Over the entire study period the monthly prevalence rate of citalopram use was higher in UK compared with NL and independent of country and age group, monthly prevalence rates were highest for citalopram low dose and very low for high dose citalopram. After the dose restrictions, in the population ≥ 65 years the use of citalopram with moderate dosage significantly decreased both in UK and NL. In UK this was also observed for the high dose in this older population, since use was low in NL a further significant decrease was not observed. Among the British and Dutch population below 65 years of age the use of high dose significantly reduced, low and moderate dosages did not decrease significantly in this age group. Monthly rates of new citalopram users were higher among the population ≥ 65 years compared to those < 65 years and reduced after the dose restrictions independent of country and age categories. Although the trends were the same, the change was only significant in the British population of ≥ 65 years (p=0.003).

Conclusions Following the dose restrictions in October 2011 the use of citalopram high and moderate dosages decreased in UK and NL. The effects seemed to be stronger in UK compared to NL. An additional effect was the decrease in elderly patients starting citalopram after the dose restrictions.

INTRODUCTION

Citalopram is a selective serotonin reuptake inhibitor (SSRI) indicated to treat depressive episodes and panic disorders and authorised in the European Union (EU) since 1989.[1] The product is available in 10 mg, 20 mg, 40 mg tablets and in a 40 mg per ml solution (oral drops). The recommended starting dose of citalopram is 20 mg daily which can be increased depending on the individual patient response, before stopping it should be gradually reduced to avoid withdrawal effects.[1] In 2011 new safety information for citalopram became available and the United States (US) Food and Drug Authority (FDA) as well as the European Medicines Agency (EMA) issued a warning for dose dependent QT interval prolongation following the use of citalopram.[2, 3] The QT interval represents the duration of ventricular depolarisation and subsequent repolarisation, and is measured from the beginning of the QRS complex to the end of the T wave.[4] A delay in cardiac repolarisation creates an electrophysiological environment that favours the development of cardiac arrhythmias, most clearly torsade de pointes, but possibly other (fatal) ventricular arrhythmias as well.[4, 5] Prolongation of the QT interval associated with a drug has led to regulatory action in the past including drug withdrawals or risk minimisation measures such as precautionary statements or prescribing restrictions.[6-8] Risk minimisation measures are defined as interventions intended to prevent or reduce the occurrence of adverse drug reactions, or to reduce their severity or impact on the patient should the adverse drug reaction occur.[9]

To minimise the risk of QT interval prolongation, the European regulatory authorities recommended reducing the maximum daily dose of citalopram from 60 mg to 40 mg and from 40 mg to 20 mg in elderly (≥ 65 years) and those with reduced liver function as they achieve higher systemic exposure to the drug than younger patients and those with normal hepatic function.[2] Furthermore, citalopram has been contraindicated for concomitant use with other medicines known to prolong the QT interval and in patients with established QT prolongation or congenital QT syndromes. A direct healthcare professional communication (DHPC) was sent to inform healthcare professionals (HCPs) at the end of October 2011.[10, 11] The product information of citalopram was updated with new safety information, dose restrictions and contraindications of citalopram.[12] The impact of these risk minimisation measures on the use of citalopram in the EU has not yet been evaluated. Therefore, the objective of this study was to assess the impact of the risk minimisation measures issued at the end of October 2011 on the use of citalopram in two European countries.

METHODS

Data sources

In this study primary care databases from two European countries were used.

The Health Improvement Network (THIN) database

THIN is a longitudinal database of primary care medical records from the United Kingdom (UK). Electronic medical records date back to 1985. The database contains anonymised medical records including data on patient demographics, medical diagnoses and prescriptions written by general practitioners (GPs), diagnoses from specialists, referrals and hospital admissions, laboratory test results, and some lifestyle characteristics as smoking and alcohol consumption. Diagnoses and symptoms are recorded using READ codes. Information on drug prescriptions is coded with MULTILEX product dictionary and British National Formulary (BNF) codes.[13] Currently, the cumulative database contains information on about 8 million patients registered with 580 practices in the UK.

Interdisciplinary Processing of Clinical Information (IPCI) database

The IPCI database is a longitudinal observational database that contains data from computer-based patient records of a selected group of GPs throughout the Netherlands (NL). The database contains information on patient demographics, drug prescriptions, clinical diagnosis, physician-linked indications for therapy, physical findings, and laboratory values (e.g. potassium, creatinine). Diagnoses and complaints are recorded using the International Classification of Primary Care (ICPC) coding system, free text and hospital discharge letters.[14] Information on drug prescription is coded according to the Anatomical Therapeutical Chemical (ATC) classification, and also the product name, quantity dispensed, dosage regimens and strength are available. In the beginning of 2013, the cumulative database contained information on about 1.6 million patients.

Study population

The study population comprised all patients registered in the THIN database between 1st January 1996 until 31 August 2013 and all patients registered in IPCI between 1st May 1998 and 31 December 2012. To be able to identify new users of citalopram, only subjects with a registration in the database of at least 365 days were included in the study. A patient was considered a new user if citalopram was prescribed after at least a previous 365 days period of non-citalopram use. Patients included in the cohort were followed from start of study period or from registration with GP plus 365 days (whichever latest) until the end of the study period, transferring out the database or death, whichever date came first.

Exposure of interest

Prescriptions of citalopram tablets (ATC code N06AB04) were identified from the THIN and IPCI database. Prescriptions of citalopram oral drops were not considered in the study since the prescribed daily dose could not be adequately calculated from the prescriptions. For each prescription the daily dose was calculated using the prescribed regimen. The daily dose was categorised in three classes i.e. ≤ 20 mg (low dose), > 20 mg to ≤ 40 mg (moderate dose), > 40 mg (high dose). Citalopram prescriptions with exactly similar prescription dates and different strengths were assumed to be used simultaneously and therefore these prescriptions were pooled and considered as one prescription (e.g. the prescriptions of a 10 mg and 20 mg tablets to reach a daily dosage of 30 mg). For each prescription the duration of citalopram exposure in person time (in days) was calculated by dividing the total number units prescribed by the number of units prescribed daily.

Outcomes of interest

To get a general picture of citalopram use we measured monthly prevalence and incidence rates of citalopram use in the total cohort. Furthermore, characteristics of patients that started citalopram before and after the recommended dose restrictions were compared to investigate whether there were differences in age at treatment initiation, sex and mean length of prescription. Compliance to the dose recommendations was reviewed by assessing changes in the distribution of the prescribed daily dose categories among all citalopram users per month. In addition, it was assessed whether patients using citalopram at time of the new dose restrictions were issued (i.e. 31 October 2011) changed the daily dose of their subsequent prescription. Those without a prescription within 30 days after the previous prescription ended were considered to have discontinued citalopram treatment.

Analysis

Monthly prevalence rates and monthly incidence rates for citalopram were calculated by dividing the number of subjects receiving at least one prescription with the total person time of the cohort and expressed per 1,000 person years (PY). Rates, including the 95% confidence interval (95% CI), were calculated and stratified by country, age categories (< 65; ≥ 65) and daily dose categories (low, moderate, high). Patients receiving prescriptions for different daily dose categories in one time period contributed to both dose categories. The proportion of citalopram users that received a citalopram prescription with a particular daily dose was calculated by dividing the number of patients using citalopram daily dose category low, moderate or high by the total number of prevalent users per month, per country and for patients aged < 65 and ≥ 65 separately. To assess the effect of the risk minimisation measures issued in October 2011 on the prevalence and incidence rates of citalopram, interrupted time series analyses were performed using an autoregressive, integrated, moving average (ARIMA [p, d ,q]) model. In this model, p represents the lingering effects of preceding scores, d is the integrated element which represents the trends in the data, and the moving average element q represents the lingering effects of preceding random shocks. The risk minimisation measures issued in October 2011 were considered the intervention and a variable was created with a value of 0 prior to the date of intervention and with a value of 1 after the date of intervention. ARIMA models were estimated prior to the intervention using the expert modeller function within SPSS, which accounted for possible seasonality within the data. This estimated model was applied on the entire set using the prevalence and incidence rate of the study drug as outcome and the intervention as independent variable. We stratified for daily dosage (low, moderate, high) and age groups (< 65 and ≥ 65). The output was the change in prevalence due to the intervention (ß) with a corresponding *p*-value. Statistical significance was assumed for two-sided *p*-values < 0.05. Interrupted time series analyses were also performed to assess the impact of the risk minimisation measures on the distribution of the daily dose among the citalopram users. The t-test or chi-square test was used to derive *p*-values when comparing continuous or categorical variables between incident citalopram users before and after the risk minimisation measures were issued. Statistical significance was assumed for two-sided *p*-values < 0.05. The interrupted time series analyses were performed using SPSS software version 15.0 (SPSS Inc, Chicago, IL, US). All other analyses were carried out using SAS version 9.2 (Cary, North Carolina, US).

RESULTS

From the UK a total number of 7,193,431 subjects were included in the cohort contributing 44,397,740 PY of follow-up between 1 January 1996 and 31 August 2013. The Dutch cohort included a total of 1,676,802 subjects contributing 4,672,494 PY of follow-up between 1 May 1998 and 31 December 2012. The study populations are described in Table 1.

Table 1: Description of the study populations

	United Kingdom	the Netherlands
Database	THIN	IPCI
Study period	1 January 1996 to 31 August 2013	1 May 1998 to 31 December 2012
Total subjects	7,193,431	1,676,802
Total person-time in PY	44,397,740 PY	4,672,494 PY
Sex, Male, N (%)	3,531,972 (49.1)	819,240 (48.9)
Mean age in years (95% CI)	40.7 (40.7 – 40.7)	39.8 (39.8 – 39.8)
Citalopram users, N (%)	492,522 (6.8)	17,465 (1.0)
Citalopram exposure in PY (%)	508,227 PY (1.1)	17,113 PY (0.4)

CI=confidence interval; IPCI=Interdisciplinary Processing of Clinical Information; PY=person year; THIN=The Health Improvement Network;

Prevalence rates

Both in the UK and NL an increase in the monthly prevalence rates of citalopram for all three daily dose categories among patients aged < 65 and ≥ 65 was observed during the study period (Figure 1a and 1b). As shown in these figures, over the entire study period the monthly prevalence rate of citalopram use was higher in UK compared with NL and in both countries the prevalence rate of citalopram was higher in elderly (≥ 65 years) compared to the population younger than 65 years of age. Independent of country and age group, the monthly prevalence rates were highest for low dose citalopram use and very low for high dose citalopram use over the complete study period. After the dose restrictions were issued in October 2011, the monthly prevalence rates of citalopram in UK did not increase any further while in NL the prevalence rate remained more or less stable (Figure 1a and 1b). Among the British elderly population, the monthly prevalence rates of moderate and high citalopram dose reduced significantly ($p<0.000$), whereas the lowest daily dose category (≤ 20 mg) among this patient population was not significantly affected ($p=0.283$). Among the Dutch elderly population a significant decrease in citalopram use was observed only for the moderate daily dose category ($p=0.012$). The use of high dose citalopram was minimal already before the warning came. Among the British and Dutch population younger than 65 years of age the use of high dose significantly reduced ($p=0.011$ and $p=0.004$), low and moderate dosages did not decrease significantly in this age group.

New citalopram users

In UK and NL the monthly incidence (new user) rates of citalopram use were generally higher among the elderly population (≥ 65 years) compared to those younger than 65 years and reduced after the dose restrictions of citalopram both in UK and NL and in both age categories (Figure 2a and 2b).
Comparing characteristics of new citalopram users before and after the dose restrictions showed that the proportion of new users aged 65 or older at treatment initiation significantly reduced 27.1% to 25.0% in NL ($p=0.026$) and from 19.1% to 17.7% in UK ($p<0.000$) (Table 2). Furthermore, among the British new citalopram users the proportion of males was significantly higher and the mean age at treatment initiation significantly lower in the period after the dose restrictions compared with the period before. No significant changes in these characteristics were observed in NL.

Figure 1a: Monthly prevalence rates of citalopram use in the Netherlands

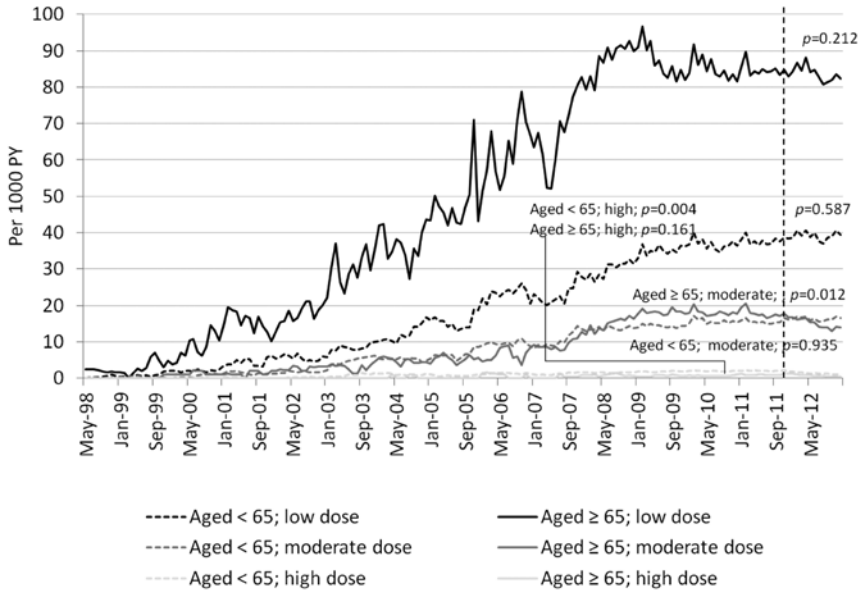
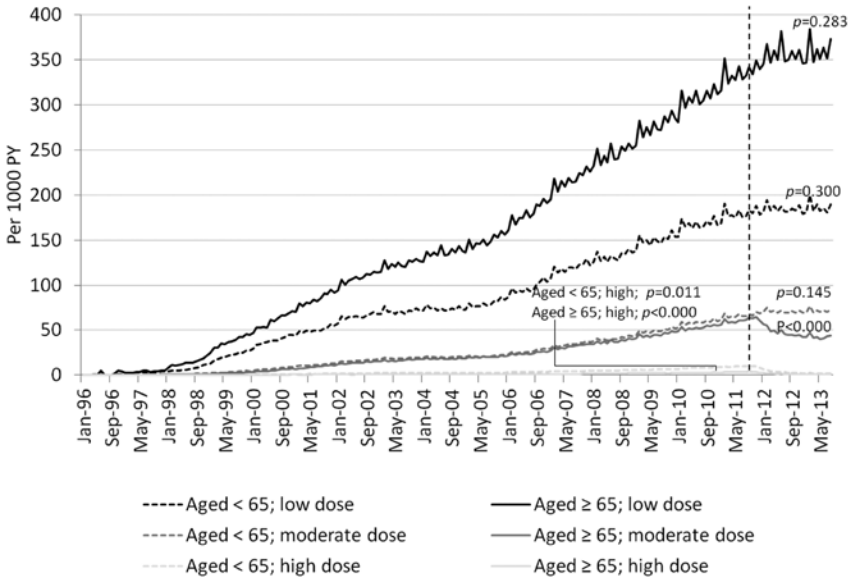


Figure 1b: Monthly prevalence rates of citalopram use in the Netherlands



The date the dose restrictions were communicated is indicated with the vertical dotted line. The p-values of the interrupted time-series analyses reflect whether subsequent observations per month after the dose restrictions were significantly affected

Table 2: Characteristics of incident citalopram users and their prescriptions in UK and the Netherlands*

	United Kingdom			The Netherlands		
	Incident users 1.Jan.1996 to 31.Oct.2011 [N=422,198]	Incident users 1.Nov.2011 to 31.Aug.2013 [N=87,664]	*p*-value	Incident users 1.Jan.1996 to 31.Oct.2011 [N=422,198]	Incident users 1.Nov.2011 to 31.Aug.2013 [N=87,664]	*p*-value
Patient characteristics at treatment initiation						
Sex, Male % (95% CI)	32.46 (32.31 – 32.60)	34.07 (33.76 – 34.39)	<0.000	36.25 (35.17 – 37.32)	36.57 (34.86 –38.28)	0.756
Mean Age (95% CI)	47.54 (47.49-47.60)	46.60 (46.48-48)	<0.000	52.23 (51.79 – 52.67)	51.70 (51.02 -52.38)	0.202
65 year or older, N; % (95% CI)	N=80,521; 19.07 (18.95 – 19.19)	N=15,537; 17.72 (17.47 – 17.98)	<0.000	N=2082; 27.10 (26.10 – 28.09)	N=765; 25.00 (23.46 – 26.54)	0.026
Prescriptions of incident users†						
Number of prescriptions	3,839,235	425,536		49,135	12,464	
Mean length per prescription, in days (95% CI)	32.29 (32.28 – 32.31)	32.21 (32.17 – 32.26)	<0.000	36.96 (36.71 – 37.22)	33.71 (33.23 – 34.18)	<0.000

CI=Confidence Interval; UK=United Kingdom.
**Incident users are patients starting citalopram after a citalopram free period of 365 days. A patient can be included as an incident user more than once and in both study periods.*
†Including prescriptions of the incident users prescribed during the corresponding period.

Figure 2a: Incidence rates of citalopram use in the Netherlands for patients aged < 65 and ≥ 65

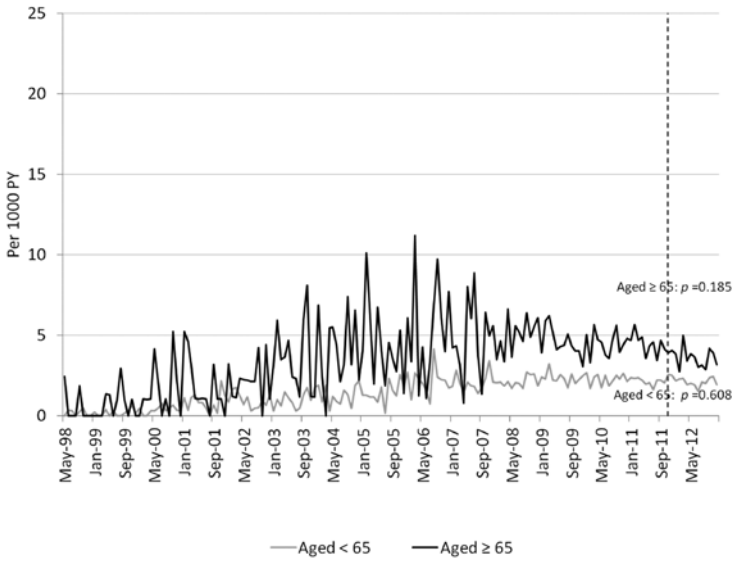
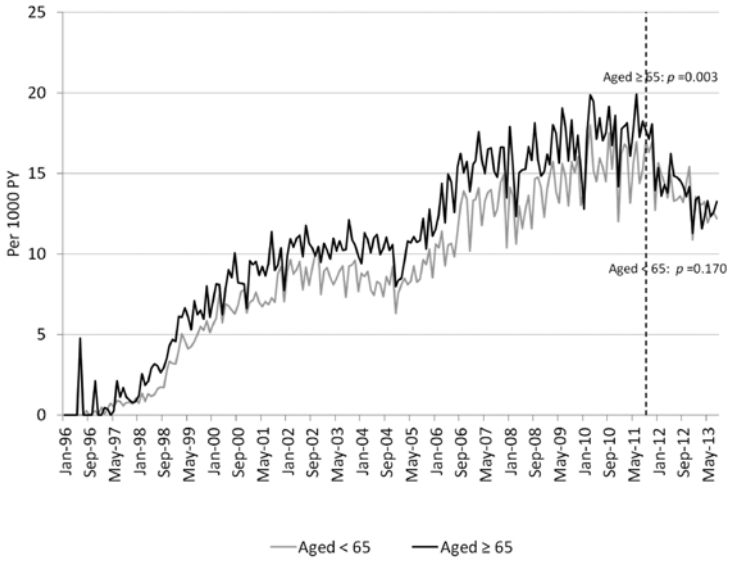


Figure 2b: Incidence rates of citalopram use in the United Kingdom for patients aged < 65 and ≥ 65



The date the dose restrictions were communicated is indicated with the vertical dotted line. The p-values of the interrupted time-series analyses reflect whether subsequent observations per month after the dose restrictions were significantly affected

Compliance to dose restrictions

No significant changes in the distribution of the three daily dose categories after the dose restrictions were recommended were observed in Dutch citalopram users (Figure 3a and 3b). In contrast, in the UK, the proportion of citalopram users that used citalopram at high daily dose significantly decreased in users aged < 65 (p<0.000) as well as among those ≥ 65 years (p=0.002) (Figure 3c and 3d). While in the older British prevalent citalopram users the proportion using moderate dosages decreased significantly after the new dose recommendations (p=0.013), this proportion significantly increased among the younger British prevalent citalopram users (p=0.048).

Figure 3a: Distribution of daily dosages in Dutch prevalent citalopram users aged < 65 years

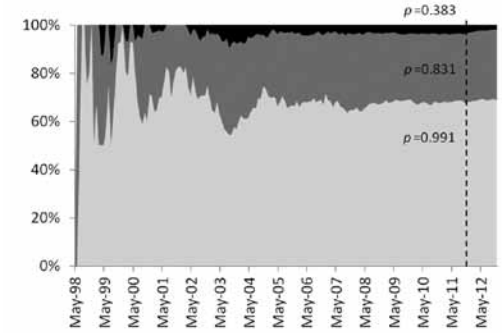


Figure 3b: Distribution of daily dosages in Dutch prevalent citalopram users aged ≥ 65 years

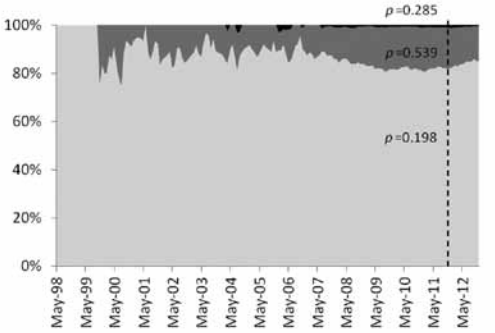


Figure 3c: Distribution of daily dosages in British prevalent citalopram users aged < 65 years

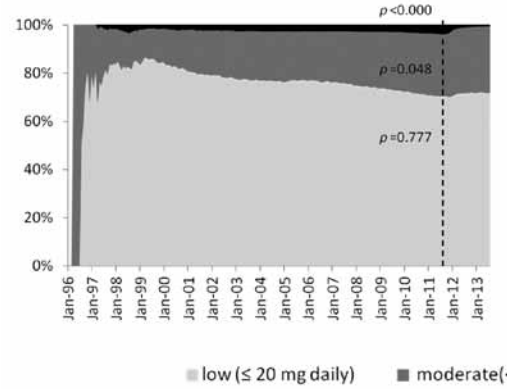
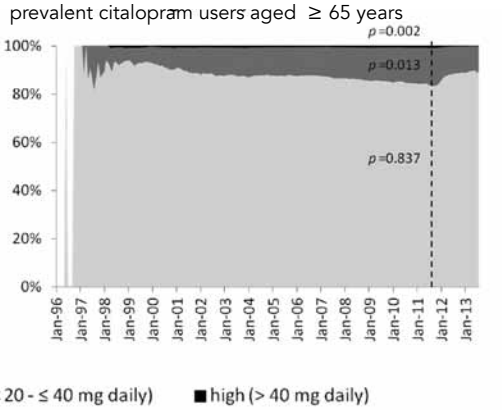


Figure 3d: Distribution of daily dosages in British prevalent citalopram users aged ≥ 65 years



The date the dose restrictions were communicated is indicated with the vertical dotted line. The p-values of the interrupted time-series analyses reflect whether subsequent observations per month after the dose restrictions were significantly affected

Table 3a and 3b show that independent of the daily dose category, the majority of citalopram users at 31 October 2011 continued the dosage that was used at 31 October 2011. Among the British, the first prescriptions (N=58,311) that followed after this date were prescribed in November 2011 (76%), December 2011 (22%), January 2012 (2%) or ≥ February 2012 (0.1%). In NL (N=3,515), these proportions were 56%, 28%, 13% and 2%, respectively. Although the largest effects were observed among patients using citalopram at high dose, still a large majority continued using this daily dose, 73.8% of the elderly and 70.4% of the users younger than 65 years in UK which was 72.7% and 73.9% in NL, respectively. The proportion of patients aged ≥ 65 that continued with citalopram in moderate daily dose was 87.3% in UK and 79.2% in NL.

Table 3a: Change in daily doses of citalopram users at 31 October 2011 in NL (N=4,034) by age category

Daily dose of prescription followed after 31 October 2011	Daily dose at 31 October 2011					
	Low Dose		Moderate Dose		High Dose	
	< 65 N=2,015 (%)	≥ 65 N=86 (%)	< 65 N=853 (%)	≥ 65 N=174 (%)	< 65 N=115 (%)	≥ 65 N=11 (%)
Discontinued*	269 (13.3)	105 (12.1	111 (13.0)	19 (10.9)	13 (11.3)	2 (18.2)
Low dose	1,691 (83.9)	752 (86.8)	25 (2.9)	8 (4.6)	1 (0.9)	-
Moderate dose	52 (2.6)	9 (1.0)	711 (83.3)	147 (84.4)	16 (13.9)	1 (9.1)
High dose	3 (0.1)	0 (0.0)	6 (0.7)	0 (0.0)	85 (73.9)	8 (72.7)

**When the last day of the prescription was followed with 30 days in which no new prescription, the patient was discontinued with citalopram*
Low dose(≤ 20 mg daily), moderate dose (>20 mg to ≤ 40 mg daily), high dose (> 40 mg daily)
NL=the Netherlands

Table 3b: Change in daily doses of citalopram users at 31 October 2011 in UK (N=64,741) by age category

Daily dose of prescription followed after 31 October 2011	Daily dose at 31 October 2011					
	Low Dose		Moderate Dose		High Dose	
	< 65 N=32,533 (%)	≥ 65 N=14,689 (%)	< 65 N=12,669	≥ 65 N=2,764 (%)	< 65 N=1,929 (%)	≥ 65 N=157 (%)
Discontinued*	4,018 (12.4)	848 (5.8)	111 (13.0)	118 (4.3)	191 (9.9)	10 (6.4)
Low dose	27,275 (83.8)	13,687 (93.2)	25 (2.9)	147 (5.3)	70 (3.6)	7 (4.4)
Moderate dose	1,181 (3.6)	150 (1.0)	711 (83.3)	2,492 (90.2)	309 (16.0)	24 (15.3)
High dose	59 (0.2)	4 (0.0)	6 (0.7)	7 (0.3)	1,359 (70.4)	116 (73.8)

**When the last day of the prescription was followed with 30 days in which no new prescription, the patient was discontinued with citalopram*
Low dose(≤ 20 mg daily), moderate dose (>20 mg to ≤ 40 mg daily), high dose (> 40 mg daily)
UK=United Kingdom

DISCUSSION

Following the dose restrictions recommended by regulatory authorities in October 2011 to minimise the risk of dose dependent QT interval prolongation in association with citalopram, in elderly the use of citalopram with moderate dosage decreased significantly both in the UK and NL and in British elderly also the use of high dose. In patients younger than 65 years, in both countries only the high dose of citalopram decreased significantly. Independent of country and age categories, a large majority of patients using citalopram at 31 October 2011 continued using the same daily dose, including high dosages. An additional effect of the risk minimisation measures was the decrease in new citalopram users of 65 year and older, which was not anticipated.

The dose restrictions seemed to have larger effect in UK than in NL. The proportion of British citalopram users that used moderate and high doses significantly reduced after the recommended dose restriction which was not significant in NL. The modest changes among Dutch prevalent users after the dose restrictions may be explained by an overall lower prevalent use of citalopram as well as the stable monthly prevalence rates in the period before the dose restrictions were issued while during this period in the UK an increasing trend of prevalent use was observed for all daily dose categories. Furthermore, the effects of dose restrictions seem to be more prominent in new users than in patients

that were already using citalopram at time of the regulatory measures and continued using citalopram. Those on treatment were less likely to have the dose changed compared to new users. These different behaviours show that different recommendations may need to be given for those that actually start treatment and those patients on treatment with a drug that needs dose escalation to avoid withdrawal symptoms.

Apart from the regulatory actions (the DHPC and updated product information) that were implemented in all EU member states, there might be other factors that potentially contributed to the changes in citalopram use or may (partly) explain differences between UK and NL. The recommended dose restrictions of citalopram were implemented in the Dutch drug prescribing and dispensing systems, the British National Formulary and NICE medicines and prescribing associates in UK shortly after they were issued.[15] These systems may have contributed to the effects on citalopram use as observed in this study. On the contrary, considering clinical guidelines, no information on maximum daily dose of citalopram was included in the Dutch GP guideline, Dutch guideline for specialists and neither in the UK guideline (NICE) for the treatment of depression and this did not change after the new dosing recommendations.[16-18] Regulatory warnings possibly lead to media attention which may affect drug prescription.[19-22] However, apart from the DHPC published at the website of the Dutch Medicines Evaluation Board and an announcement of the Netherlands Pharmacovigilance Centre,[23] there was no media attention with regard to the QT interval prolongation of citalopram neither escitalopram in NL. In the UK the Medicines and Healthcare products Regulatory Agency (MHRA) published information on the new dose recommendations for citalopram on their webpage in a Drug Safety Update and updated their learning module on SSRIs.[24, 25] Information on the issue in the British newspapers was limited and only appeared a few months later, in July 2012 and January 2013.[26-28]

Strengths and limitations

This study used two primary care databases which contain a large number of patients, reflect the underlying population and allowed the evaluation of a 14 to 16 year period. A major advantage of the study was also that we studied the impact in two European populations while using same definitions and analysis. This enabled us to directly compare the effects of the risk minimisation measures on citalopram use across two countries. Interrupted time series design is preferred to study the impact of policy changes where it difficult to employ a control group, and account for potential biases in the effect of the intervention including secular trend, seasonal effects, random fluctuations and autocorrelations.[29]

Since in our study primary care data was used there are several limitations. We could only assess the impact of the recommended dose restrictions on prescription of citalopram by GPs. Prescriptions from specialists were not included but previous research has shown that in NL and other western countries the majority of the SSRIs are prescribed by GPs.[19, 30, 31] A further limitation of the study is that not all aspects of the risk minimisation measures communicated in October 2011 were evaluated. We did not assess compliance with the contraindication of concomitant use with other drugs known to prolong the QT interval. More importantly, the impact on the occurrence of QT interval prolongation in citalopram users has not been studied while minimising this risk was the primary aim of the risk minimisation measures. Future research should study the impact of the risk minimisation measures on the occurrence of prolonged QT interval or other relevant outcomes such as torsades de pointes, ventricular arrhythmia or sudden cardiac death.

Conclusions

After the risk minimisation measures were issued in October 2011, the use of high and moderate dose citalopram decreased in both UK and NL, although stronger in UK. While in both countries the decrease in elderly people starting citalopram after the dose restrictions was considered an additional effect, changes in prescriptions of patients that were using citalopram at time of the regulatory action were limited. It might be that the overall higher and up until than increasing prevalent use of citalopram in UK before October 2011 resulted in stronger visible effects compared to NL but it may also be possible that the British prescribers react more prompt to regulatory warnings compared to the Dutch prescribers.

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6

A COMPARISON OF PREGNANCY PREVENTION PROGRAMMES IN EUROPE

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ABSTRACT

Background Pregnancy Prevention Programmes (PPP) can be imposed by regulatory authorities to minimise the risk of exposure to teratogenic drugs during pregnancy, thus preventing congenital anomalies. The objective of this study was to explore the reasons to request PPPs in the EU and the elements that these programmes included.

Methods For the seven drugs with a PPP, the Summary of Product Characteristics (SmPC) and publicly available assessment reports at the EMA website were used to obtain data.

Results Five of the seven drugs obtained a PPP based on an established or expected high teratogenic risk in humans. Similarities in the PPPs were: pregnancy tests both before and monthly during drug use; contraceptive use and pregnancy prevention counselling. Differences regarded educational materials, restricted drug supply, continuation of contraceptive use and pregnancy tests after treatment discontinuation. The last two differences could be explained by pharmacological characteristics of the drug.

Conclusions The reason for requesting a PPP is not always clearly defined and variation in risk minimisation measures for teratogenic drugs exists. There is a need for regulatory guidance on proper judgment to request for a PPP and its development. Knowledge on the benefits and burden of PPPs in clinical practice is necessary to optimise PPPs.

INTRODUCTION

Teratogenicity of a drug is a risk that can significantly impact its benefit-risk balance due to the occurrence of congenital anomalies when used shortly before or during pregnancy. Teratogens can irreversibly modify growth, structure, or function of the developing embryo or fetus.[1] A well-known teratogenic drug is thalidomide. Thalidomide was introduced at the European market in the late 1950s as sedative and morning-sickness treatment. In 1961, it was discovered that thalidomide caused congenital anomalies in new-borns of women who had taken thalidomide during pregnancy and subsequently the drug was withdrawn.[2, 3] Since there is a very low tolerance for teratogenic drug exposure in pregnant women, it becomes important to minimise the risk with appropriate measures to improve the benefit-risk balance of teratogenic drugs.

Risk minimisation measures are interventions that aim to minimise the occurrence or severity of safety concerns related to a drug.[4] Routinely required risk minimisation measures are the Summary of Product Characteristics (SmPC), the package leaflet (PIL), pack size and legal (prescription) status, which are considered sufficient for most drugs. However, some drugs contain serious important risks requiring an extra form of risk minimisation, that is, additional risks minimisation measures (aRMMs).[4] An example of an aRMM is a pregnancy prevention programme (PPP), which can be required to minimise the risk of exposure to teratogenic drugs during pregnancy to prevent congenital anomalies.

Currently there are seven drugs for which a PPP is required in the European Union (EU). In 2008 thalidomide was reintroduced as treatment for multiple myeloma with strict risk minimisation measures including a PPP that should be implemented.[5] In addition to thalidomide, another immunosuppressant, lenalidomide, also has a PPP as well as isotretinoin, acitretin and alitretinoin (vitamin A derivatives), bosentan and ambrisentan (endothelin receptor antagonists [ERAs]). Elements and tools that can be part of a PPP include educational programmes for prescribers and patients, concomitant use of contraception and the need for pregnancy tests before and during treatment on a monthly basis. In clinical practice different stakeholders can be involved with the PPP, for example, patients, physicians, pharmacists and wholesalers.[6] Implementation of a PPP in clinical practice can impose additional burden on patients and the healthcare system. To avoid unnecessary and ineffective measures, the PPP should be carefully justified, drafted and monitored after implementation.

Currently, clear guidance or criteria when and which aRMMs should be required remains limited and decisions are usually made on a case-by-case basis. PPPs should only be imposed to minimise clearly defined serious safety concerns but there might have been different rationales for the currently implemented PPPs. Furthermore, there is no standard PPP and the PPPs currently in place may, therefore, consist of different elements and recommendations which could potentially lead to confusion and diminished compliance by prescribers, patients or other stakeholders. The aim of this research was to review the regulatory rationale and criteria to require a PPP in the EU and to describe the different elements included in the existing PPPs in the EU.

METHODS

Regulatory rationale to require PPPs

The rationale to require a PPP was assessed for the seven drugs with a PPP in the EU using publicly available information from the summary of product characteristics (SmPC) as available on 5 August 2011. The SmPCs were obtained either from the European Public Assessment Reports (EPAR) via

the European Medicines Agency (EMA) website[7] or from the Heads of Medicines Agencies (HMA) website.[8] In addition, for the centrally authorised products the scientific discussion presented in the EPAR was reviewed.

For each drug included in this study the following information was identified: the active substance, indication for use, date of authorisation and drug half-life. Information on teratogenicity was taken verbatim from SmPC Section 4.6 'fertility, pregnancy and lactation', Section 5.3 'preclinical safety data' and from the scientific discussion presented in the EPAR.

PPP elements

The approved SmPC of each drug and, if available, Annex II 'Conditions and restrictions of the marketing authorisation' were reviewed to identify elements of the currently approved PPPs. An annex II includes conditions and restrictions regarding the safe and effective use of the medicinal product as agreed in the RMP and is available for centrally authorised products and drugs assessed in regulatory referral procedures (isotretinoin).

Drug exposure

For each drug of interest the exposure was identified in the EU-ADR network and the InterActionDataBase (IADB). The EU-ADR network consists of anonymous drug prescription or dispensing information of approximately 30 million individuals from seven population-based electronic healthcare databases of four European countries (Denmark, Italy, the Netherlands and the United Kingdom).[9] The IADB is a Dutch community pharmacy database and contains prescriptions of approximately 600,000 individuals.[10]

The total drug exposure was identified for each drug of interest per calendar year and presented for both data sources separately. The drug exposure in EU-ADR network databases was calculated in person-years for the period 2000 - 2010. For each prescription, the exposure in person time (days) was calculated by dividing the total number of units prescribed by the number of units prescribed daily. Per calendar year, the sum of the exposed person time in days was divided by 365.25 to convert the exposure unit to person-year. Drug exposure in the IADB was identified by counting the number of patients who received the drugs under study during the period 2000 - 2009. Alitretinoin may not be marketed during 2000 - 2010 which resulted in no drug exposure for this drug in neither EU-ADR network nor the IADB.

Women of childbearing potential (WCBP), defined as female patients between 15 and 49 years of age, exposed to the drugs under study, were identified in both data sources. Besides the total drug exposure per calendar year, for each drug the percentage of drug exposure covered by WCBP was calculated by dividing the exposed WCBP by the total drug exposure of each drug.

Descriptive statistics were used to calculate the drug exposure.

RESULTS

Drug specific information for all drugs with a PPP in the EU is presented in Table 1. According to the SmPCs of the drugs, the vitamin A derivatives are authorised for dermatological indications, such as severe forms of acne, psoriasis and chronic hand eczema. The immunosuppressants thalidomide and lenalidomide are currently authorised to treat the orphan indication multiple myeloma. Both ERAs,

bosentan and ambrisentan, are indicated to treat pulmonary arterial hypertension (PAH). Bosentan is also licensed to treat systemic sclerosis.

Regulatory rationale to require PPPs

Teratogenicity in humans is established for thalidomide and based on structural and pharmacological similarities and pre-clinical evidence; teratogenicity in humans is expected for lenalidomide. An established high risk for congenital anomalies in humans is known for vitamin A derivatives and determined for isotretinoin. For all three retinoids (isotretinoin, acitretin and alitretinoin) teratogenic effects have been observed in animal studies. In contrast, for the ERAs (bosentan and ambrisentan), teratogenicity has only been observed in animal studies and implications for humans were unknown at the time of licensing and are still not fully known. The scientific information from the EPAR and the SmPC of bosentan described that PAH severely deteriorates during pregnancy, and that the disease itself and the teratogenicity in animals did lead to a contraindication for bosentan use during pregnancy. For ambrisentan, according to the EPAR, the availability of alternative therapeutics was also reason to contraindicate use during pregnancy.

Review of PPP elements

The elements of the seven PPPs are summarised in Table 2. Common elements in all PPPs included: a contraindication for use during pregnancy and for WCBP unless conditions of the PPP are met; required pregnancy tests before treatment initiation and monthly during treatment; need for contraceptive measures; patient counselling on pregnancy prevention. All seven drugs had educational material in addition to the SmPC and package leaflet for prescribers and patients

The continuation of contraceptive use and performance of pregnancy tests after treatment discontinuation varies per drug, that is, not at all, for a 4 weeks period or up to 1 year. These variations are due to pharmacological differences such as the drug half-life or the metabolite half-life. Other differences observed were additional educational material targeted to the pharmacist, which was only required for isotretinoin and alitretinoin. Furthermore, only three PPPs included a patient card. Dispensing restrictions were limited to three PPPs. Confirmation of the patient's understanding of the teratogenic risk to be obtained by the prescriber was part of four PPPs.

An interesting difference was identified for the generic formulations of acitretin, authorised through decentralised procedure (DCP), which have educational material in addition to the SmPC and package leaflet whereas for the reference product (nationally authorised) only the SmPC provide information on the PPP and no educational materials are involved.

Comparison of the SmPCs of the seven drugs, showed that references to the PPP were made in different SmPC sections, that is, Section 4.4 'Precautions and warnings' or Section 4.6 'Pregnancy and lactation' or both.

Drug exposure

Tables 3 and 4 present the total drug exposure and percentage covered by WCBP in the EU-ADR databases and the IADB, respectively. As expected, isotretinoin and acitretin both were more widely prescribed, in general, as well as among women of childbearing potential, compared to the orphan drugs, thalidomide, lenalidomide, bosentan and ambrisentan.

Table 1: Information on drugs with a PPP in the EU

Immunosuppressants		Retinoids (Vitamin A derivatives)			Endothelin receptor antagonists (ERAs)	
Active substance						
Thalidomide	Lenalidomide	Isotretinoin	Acitretin	Alitretinoin	Bosentan	Ambrisentan
*Authorisation date in EU**						
16 April 2008	14 June 2007	25 April 1984	26 October 1989	14 April 2009	15 May 2002	21 April 2008
*Authorisation procedure**						
Central	Central	MRP	National†	DCP	Central	Central
Indication						
Multiple myeloma. Thalidomide is prescribed and dispensed according to the PPP.	Multiple myeloma.	Severe forms of acne.	Severe extensive psoriasis. Severe congenital ichthyosis. Severe Darier's disease	Sever chronic hand eczema.	Pulmonary arterial hypertension. To reduce the number of new digital ulcers in patients with systemic sclerosis.	Pulmonary arterial hypertension.
Half-life time in hours						
5.5 - 7.3	3 - 3.5	19 - 29	50 - 123	2 - 10	5.4	13.6 - 16.5
Information on teratogenicity and reasons for PPP‡						
Thalidomide is a powerful human teratogen, including a high frequency (30%) of severe and live threatening birth defects. Animal studies have demonstrated differences in species susceptibility to the teratogenic effects of thalidomide.	The structural and pharmaco-logical similarity to thalidomide, which is a known human teratogen. Lenalidomide induced in monkeys malformations similar to those described with thalidomide. Therefore, the teratogenic effect of lenalidomide is expected.	Risk of congenital malformations after isotretinoin use. Like other retinoids, isotretinoin has been shown to be teratogenic in animals.	It is known that retinoids can cause serious congenital abnormalities in humans. As vitamin A and other retinoids, acitretin can cause malformations in the offspring of various animal species (rats, mice and rabbits), even at dose levels recommended for humans.	Alitretinoin is a retinoid and therefore is a potent teratogen. Like other retinoids, alitretinoin has been shown to be teratogenic *in vitro* and *in vivo*.	Teratogenic effect of bosentan has been shown in animal studies (in rats, not in rabbits). There are no reliable data on the use of bosentan in pregnant women. The potential risk for humans is still unknown. The similarity of the pattern of malformations in endothelin receptor knockout mice and other ERAs, indicate that this is a class effect. In the context of PAH, pregnancy must be avoided since it leads to cardiovascular stress with harmful consequences to pregnant women.	Animal studies (rats and rabbits) have shown that ambrisentan is teratogenic. There is no experience in humans. Teratogenicity is a suspected class effect. Evidence of a known direct pharmacologic effect leading to malformations, and the availability of alternative therapeutics for PAH.

DCP=Decentralised procedure; EU=European Union; MRP=Mutual recognition procedure; PAH=pulmonary arterial hypertension; PPP=pregnancy prevention programme.
**Of the innovator products.*
†Generic acitretin-containing products have been licensed through DCP.
‡ from SmPC Section 4.6 'fertility, pregnancy and lactation', Section 5.3 'preclinical safety data' and the scientific discussion presented in the European Public Assessment Report.

Table 2: Elements of the PPPs identified from SmPC and Annex II 'Conditions and restrictions of the marketing authorisation'

Active substance	Thalidomide	Lenalidomide	Isotretinoin	Acitretin	Alitretinoin	Bosentan	Ambrisentan
Contraindication during pregnancy and for WCBP unless following PPP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Need for contraception for WCBP	4 weeks before therapy until 4 week after discontinuation; Combined oral contraceptives are not recommended because of increased risk of VTE in patients with multiple myeloma.	4 weeks before therapy until 4 week after discontinuation; Combined oral contraceptives are not recommended because of increased risk of VTE in patients with multiple myeloma.	4 weeks before therapy until 4 weeks after discontinuation; In addition to a non-barrier method, a barrier method is advised.	4 weeks before therapy until 2 years after discontinuation; In addition to a non-barrier method, a barrier method is advised.	4 weeks before therapy until 4 weeks after discontinuation; In addition to a non-barrier method, a barrier method is advised.	Practice reliable contraception during treatment; Since hormonal contraceptive interact with bosentan, a barrier method is advised in addition to a non-barrier method.	Practice reliable contraception during treatment.
Negative pregnancy test for WCBP	Prior to therapy; monthly during therapy; 4 weeks after discontinuation.	Prior to therapy; monthly during therapy; 4 weeks after discontinuation.	Prior to therapy; monthly during therapy; 5 weeks after discontinuation.	Prior to therapy; monthly during therapy; 1-3 monthly until 2 years after discontinuation.	Prior to therapy; monthly during therapy; 5 weeks after discontinuation.	Prior to therapy; monthly during therapy.	Prior to therapy; monthly during therapy.
Patient counselling on pregnancy prevention	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Precautions for male patients	The use of condoms since thalidomide is present in human semen.	The use of condoms since lenalidomide is present in human semen.	Transmission via the male is considered negligible.	Transmission via the male is considered minimal.	Transmission via the male is considered negligible.		
No blood donation during and for a week after treatment	Yes	Yes	Yes	WCBP may not receive blood of patients treated with acitretin	Yes		
Confirmation of understanding the risk and precautions and/or appropriate counselling has taken place	Treatment Initiation Forms.	Via patient card and checklist for physician.	Informed consent form.		Informed consent form.		

Active substance	Thalidomide	Lenalidomide	Isotretinoin	Acitretin	Alitretinoin	Bosentan	Ambrisentan
Prescription restriction for WCBP	Limited to 4 weeks; Continuation requires new prescription; Negative pregnancy test before initiation.	Negative pregnancy test before initiation.	Limited to 30 days; Negative pregnancy test before initiation or continuation	Limited to 30 days; Negative pregnancy test.	Limited to 30 days; Negative pregnancy test before initiation or continuation.	Negative pregnancy test before initiation.	Limited to 30 days; Negative pregnancy test before initiation.
Dispensing restrictions for WCBP	Should be filled within 7 days after prescription		Should be filled within 7 days after prescription. humans.		Should be filled within 7 days after prescription.		
Education material regarding PPP for:	Prescribers: *brochure* Patients (WCBP and males): *brochure, patient card*	Prescribers: *brochure, checklist* Patients (WCBP and males): *brochure, patient card*	Prescribers: *brochure* Pharmacist: *brochure* All patients: *brochure*	No*	Prescribers: *brochure* Pharmacist: *brochure* All patients: *brochure*	Prescribers: *brochure* All patients: *brochure*	Prescribers: *brochure, pre-prescription checklist* All patients: *brochure, patient reminder card* Male partners of WCBP: *brochure*
SmPC specifically mentions the existing educational programme or PPP	Referred to PPP and educational material	Referred to PPP and educational material	Referred to PPP and educational material	No	Referred to PPP and educational material	No	No
SmPC section that provides information about PPP	4.4	4.4	4.4	4.6	4.4	4.4 and 4.6	4.4 and 4.6

PPP=pregnancy prevention programme; SmPC=Summary of product characteristics; WCBP=Women of childbearing potential; VTE=Venous thrombotic embolism.
**The SmPCs of acitretin-containing products authorised through DCP do refer to educational materials.*

Table 3: Exposure of drugs with a PPP in person-years identified from the EU-ADR databases*

	Thalidomide		Lenalidomide		Isotretinoin		Acitretin		Bosentan		Ambrisentan	
Year	Person years exposed	Percentage covered by WCBP†	Person years exposed	Percentage covered by WCBP†	Person years exposed	Percentage covered by WCBP†	Person years exposed	Percentage covered by WCBP†	Person years exposed	Percentage covered by WCBP†	Person years exposed	Percentage covered by WCBP†
2000	0.3	34%	-	-	865.8	37%	263.8	11%	-	-	-	-
2001	1.1	12%	-	-	1758.6	39%	376.5	11%	-	-	-	-
2002	2.4	0%	-	-	1883.1	39%	382.3	10%	-	-	-	-
2003	3.7	0%	-	-	1909.8	39%	411.3	10%	0.2	35%	-	-
2004	6.0	1%	-	-	2547.2	44%	554.9	9%	15.5	8%	-	-
2005	5.3	0%	-	-	2354.5	41%	536.3	8%	27.7	14%	-	-
2006	6.7	0%	-	-	2067.6	39%	576.6	7%	42.3	16%	-	-
2007	7.3	4%	0.6	0%	2049.6	36%	610.0	8%	56.3	18%	-	-
2008	11.8	2%.	13.2	0%	1694.0	35%	604.1	7%	90.0	20%	0	0%
2009	22.8	3%	12.8	0%	462.9	33%	178.8	8%	1.6	14%	0	0%
2010	4.4	0%	1.2	0%	40.0	35%	12.2	5%	0.8	0%	0	0%
Total	71.9	2%	27.8	0%	17863.2	39%	4640.9	9%	232.7	17%	0	0%

WCBP=women of childbearing potential

**EU-ADR databases include databases from Denmark, Italy, the Netherlands and United Kingdom. Alitretinoin was not marketed until 2010 and therefor not included in the table*

† Percentage of patient-years covered by women of childbearing potential, that is, female patients between 15 and 49 years of age.

Table 4: Number of patients exposed to drugs with a PPP identified from the Dutch IADB.nl database*

	Thalidomide		Lenalidomide		Isotretinoin		Acitretin		Bosentan		Ambrisentan	
Year	Number of patients exposed	Percentage covered by WCBP†	Number of patients exposed	Percentage covered by WCBP†	Number of patients exposed	Percentage covered by WCBP†	Number of patients exposed	Percentage covered by WCBP†	Number of patients exposed	Percentage covered by WCBP†	Number of patients exposed	Percentage covered by WCBP†
2000	1	0%	-	-	413	33%	150	12%	-	-	-	-
2001	2	0%	-	-	360	34%	133	15%	-	-	-	-
2002	0	0%	-	-	365	32%	127	13%	-	-	-	-
2003	2	50%	-	-	394	30%	158	17%	0	0%	-	-
2004	3	0%	-	-	336	33%	177	17%	0	0%	-	-
2005	1	100%	-	-	306	27%	145	11%	0	0%	-	-
2006	2	0%	-	-	333	31%	143	9%	0	0%	-	-
2007	6	0%	2	0%	304	31%	141	11%	0	0%	-	-
2008	1	0%	13	0%	331	35%	135	7%	2	0%	0	0%
2009	16	0%	10	0%	361	33%	124	7%	0	0%	0	0%

WCBP=women of childbearing potential

** alitretinoin was not marketed until 2010 and therefore not included in the table*

† Percentage of patients covered by women of childbearing potential, that is, female patients between 15 and 49 years of age.

DISCUSSION

In the EU, the PPPs of thalidomide, lenalidomide and the vitamin A derivatives have been imposed based on an established or expected high teratogenic risk in humans. For bosentan and ambrisentan, the reasoning for the imposed PPP was less clear. The PPPs contained common elements in all PPPs such as a contraindication during pregnancy, the need for contraception and regular pregnancy tests. Differences between PPPs were observed with respect to the additional educational material and restricted drug supply. Both the total drug exposure and exposure among WCBP were the highest for isotretinoin.

The indication of a drug might explain the different percentages of use among WCBP. For instance, isotretinoin is indicated to treat severe forms of acne which frequently concerns WCBP while thalidomide is indicated for the treatment of multiple myeloma, a disease which occurs at an older age. The fact that teratogenic effects of vitamin A derivatives are established and that patients treated with these drugs relatively frequent concerned WCBP, stresses the importance for adequate measures to prevent exposure during pregnancy in this patient population.

For the ERAs, teratogenicity has only been shown in animals, but the indication of the drug, PAH, is known to severely deteriorate during pregnancy.[11] The need for a PPP may be open for discussion since risk minimisation measures are intended to minimise drug-related risks while for the ERAs the disease related risk, together with evidence from animal studies, might have led to a PPP.[4] A comparable disease-related risk is present for other drugs indicated for PAH, for example, sildenafil and tadalafil. However, in contrast with the ERAs, animal studies do not indicate direct or indirect harmful effects on embryonal or foetal development for sildenafil and tadalafil,[12, 13] which might explain why these drugs neither have a PPP nor a contraindication for use during pregnancy. The non-clinical evidence for embyonal or foetal toxicity for the ERAs and the availability of alternative PAH therapies besides the ERAs, seems to have led to a PPP and may explain the stricter risk minimisation measures for the ERAs compared to other PAH therapies.

For some drugs with known teratogenicity in animals or humans a PPP has not been requested but risk minimisation measures are restricted to a contraindication for use during pregnancy and warnings in the SmPC, for example, for methotrexate.[14] Although these drugs do not have a formal PPP, some restrictions are imposed on these drugs by the SmPC, such as a negative pregnancy test before treatment initiation in WCBP and a recommendation to use effective contraception during treatment.[14-17] For fingolimod and leflunomide these recommendations are also addressed with aRMMs, however, a formal PPP has not been requested.

There are also several drugs with a known teratogenic risk in humans which neither have a PPP nor a contraindication for use during pregnancy such as antiepileptic drugs valproic acid or carbamazepine.[18, 19] Once women with these medical conditions are planning to become pregnant antiepileptic treatment options should be carefully reviewed and potential treatment benefits should be weighed against the possible harms for the developing fetus. Although a PPP seems standard for high teratogenic drugs as thalidomide and the vitamin A derivatives, variation in the rationale to request PPPs, aRMMs or contraindication pregnancy for teratogenic drugs was observed.

The EU '*Guideline on risk assessment of medicinal products on human reproduction and lactation:* from data to labelling' describes factors to be considered in the assessment of SmPC wordings regarding drug use during pregnancy, that is, contraindication, warnings and recommendations.[20] Factors to be considered include human experience, relevant non-clinical studies, possible alternative safer

treatment options and the possibility to delay treatment until the pregnancy has ended. It is difficult to assess whether these factors can explain the variation in the risk minimisation measures taken for teratogenic drugs observed in this study or whether inconsistent regulatory decisions were made. The current EU guideline does not address reasons for requesting a PPP or possible elements to be included in a PPP. Further regulatory guidance on these topics would be relevant for the assessment and development of PPPs, especially for new drug classes. Recently, a PPP has been requested for the first drug of the new drug class of Hedgehog pathway inhibitors, that is, vismodegib, indicated for basal cell carcinoma.[21]

PPP elements

The first PPP in the EU was established for isotretinoin in 1988 and in 2003 the European Commission released a harmonised EU PPP for this drug.[22] This PPP seems to be used as a starting point in the development of the PPPs of the other drugs, which resulted in similarities between the PPPs, especially for comparable drugs as the other retinoids. Variety in the period to continue contraceptive use and regular pregnancy tests after drug discontinuation, can be explained by drug-specific characteristics as the drug half-life or its metabolites. However, differences in drug dispensing restrictions (i.e., drug dispensing within 7 days after prescription; prescription restricted to 30 days) and variation in the type of educational materials used (initiation forms, patient cards) which were aimed at different target groups (the pharmacist was not always involved) are difficult to explain. The absence of regulatory guidance on PPPs and the fact that PPPs can be designed on a case-by-case level, possibly explain the variation in regulatory decisions.

Benefits and burden of the PPP

A consequence of implementing a PPP in clinical practice is the increased burden on the patient and healthcare system with extra administrative tasks, use of risk minimisation tools and monthly consultations with patients. Whether this burden can be accepted depends on the benefits and the existing alternatives of a PPP. Knowledge on the actual benefits and burden of the different PPPs is however limited. Different outcome measures can be used to indicate PPP effectiveness in clinical practice. Preferably, both the occurrence of drug exposure during pregnancy (known as the 'final outcome measure') as well as the compliance to PPP elements (the so called 'process indicators') should be used.[23] The latter includes evaluation of prescriber's and patients' behavior with regard to the PPP requirements, for example, length of isotretinoin prescription or concomitant prescription of contraceptives and conclusions on occurrence of drug exposure during pregnancy could not be drawn. Studies on the effectiveness of PPPs in the US and EU concluded that compliance to PPPs (e.g., rate of contraceptive use) could be improved, but conclusions on the pregnancy rates were less clear.[24, 25] The effectiveness of the monthly pregnancy tests during isotretinoin use has been studied and seems not to reduce the pregnancy exposure rate, whereas the regular pregnancy tests considerably contributes to the burden of the PPP.[26] Different versions of the isotretinoin PPP in the US have been evaluated. In 2002, SMART (System to Manage Accutane Related Teratogenicity) was implemented but due to dissatisfied results an even stricter PPP, iPLEDGE, has been implemented since 2006. Both SMART and iPLEDGE did not result in reduced number of isotretinoin exposed pregnancies in the US as compared to the PPP implemented before 2002, even though compliance to the stricter requirements had increased.[27-29] Thus, a more stringent PPP does not guarantee better results with regard to pregnancy exposure rates, while it may place an unnecessary additional burden on the stakeholders.

There might be a maximum threshold for the effectiveness of PPPs and more strict programmes may not have additional effect. Although it may not be possible to completely eliminate drug exposure

shortly before and during pregnancy, this should be reduced to a minimum. Considering the expected burden of the PPP and the fact that drugs as thalidomide, lenalidomide and the ERAs are rarely prescribed to WCBP due to the indication,[30-32] the need for a PPP for these drugs may be open for discussion. Especially for the ERAs since the reason for the PPP seems less clear as compared to high teratogenic drugs. It can be questioned whether a PPP is the most efficient tool to prevent pregnancies for these rarely prescribed drugs and there might be solutions that limit the burden of the PPP.

Strengths and limitations

Only the PPPs implemented in the EU have been reviewed in this study which limits the generalisability of this study. Since legal bases and regulatory systems differ across countries and continents, this study focused on the PPPs in the EU to be able to provide recommendations targeted at the EU regulatory system. Comparisons of the PPPs and the effectiveness of these programmes between the different continents might be quite interesting.

This study provides a comparison of the PPPs currently implemented in the EU. It would be relevant to study the benefits and burdens of single PPP elements to be able to implement the most efficient PPPs. This might even differ between countries.

Recommendations

PPPs are developed on a case by case basis, however, knowledge and guidance on when requesting a PPP and the content of a PPP is limited. During the assessment of the need for a PPP and the development of such a programme, drug-specific characteristics, previous experiences as well as the feasibility in clinical practice should be considered by involving stakeholders, for example, prescribers, pharmacists and patients. It may be helpful to provide guidance on standard requirements and optional elements of PPPs in the European guideline on human reproduction and lactation. Furthermore, to facilitate compliance in clinical practice, PPPs should be easy to be adhered to and understandable for stakeholders. Due to differences in healthcare systems, the roles and responsibilities of prescribers and pharmacists may vary between EU member states and national adjustments might be necessary. Possibilities for harmonisation at national level are both the type of educational tools and the content of these materials, which currently vary a lot among the different drugs.

Conclusions

Risk minimisation measures for teratogenic drugs can vary. The reasons for requiring a PPP seems not consistent for drugs that currently have a PPP in the EU. Differences between the existing PPPs in the EU are identified which not all could be explained. There is a need for more and better regulatory guidance on requesting a PPP and knowledge on the benefits and burden of PPP elements in order to develop optimal PPPs.

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7

ISOTRETINOIN EXPOSURE DURING PREGNANCY: A POPULATION-BASED STUDY IN THE NETHERLANDS

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ABSTRACT

Objective To estimate isotretinoin exposure in Dutch pregnant women despite the implemented pregnancy prevention programme (PPP) and second, to analyse the occurrence of adverse fetal or neonatal outcomes in these isotretinoin exposed pregnancies

Design Population-based study

Setting The Netherlands

Participants A cohort of 203,962 pregnancies with onset between 1 January 1999 and 1 September 2007 consisting of 208,161 fetuses or neonates.

Main outcome measures Isotretinoin exposure in the 30 days before or during pregnancy. Proportions of adverse fetal or neonatal outcomes, defined as intrauterine deaths ≥ 16 week of gestation and neonates with major congenital anomalies. Odds ratios (ORs) with 95% confidence intervals (CI) adjusted for maternal age were calculated to estimate the risk of adverse fetal or neonatal outcome after maternal isotretinoin exposure.

Results 51 pregnancies, 2.5 (95% CI 1.9 to 3.3) per 10,000 pregnancies, were exposed to isotretinoin despite the pregnancy prevention programme. Forty-five of these pregnancies, 2.2 (95% CI 1.6 to 2.9) per 10,000 pregnancies, were exposed to isotretinoin during pregnancy and six additional women became pregnant within 30 days after isotretinoin discontinuation. In 60% of isotretinoin exposed pregnancies, women started isotretinoin while already pregnant. In five out of the 51 isotretinoin exposed pregnancies (53 fetuses), 9.4% (95% CI 1.3% to 17.6%), had an adverse fetal or neonatal outcome. The OR for adverse fetal or neonatal outcomes after isotretinoin exposure in 30 days before or during pregnancy was 2.3 (95% CI 0.9 to 5.7) after adjustment for maternal age.

Conclusions Although a PPP was already implemented in 1988, we showed that isotretinoin exposed pregnancies and adverse fetal and neonatal events potentially related to the exposure still occur. These findings from the Netherlands add to the evidence that there is no full compliance to the isotretinoin PPP in many Western countries. Given the limited success of iPLEDGE, the question is which further measures are able to improve compliance.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first population-based study in the European Union (EU) on isotretinoin exposure during pregnancy in a large cohort of more than 200,000 pregnancies which enabled estimating isotretinoin exposure rates among pregnant women and its consequences on a nationwide scale.
- From the virtually complete and detailed drug dispensing data, isotretinoin exposure could only be estimated since drug dispensing data does not ascertain actual drug use and precise exposure intervals. However, patients coming for refills are usually taking their drug.
- Spontaneous abortions before gestational age of 16 weeks and elective abortions were not included in our cohort and therefore our results probably underestimate the number of isotretinoin exposed pregnancies and its consequences.
- Specific teratogenic risks could not be estimated with data lacking information on pregnancies until 16 weeks of gestation and lacking detailed descriptions of adverse fetal and neonatal outcomes.

INTRODUCTION

Isotretinoin, a vitamin A derivative, is licensed in the European Union (EU) since 1983 and is indicated for systemic treatment of severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) in patients resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.[1] The teratogenic potential is an important characteristic of isotretinoin. Animal studies already suggested teratogenic effects in humans and isotretinoin has been contraindicated for use during pregnancy since the very beginning of the marketing authorisation. Despite this contraindication, the first cases of congenital anomalies after isotretinoin use during pregnancy were documented already in 1983.[2] As described by Lammer et al. in 1985, isotretinoin embryopathy consists of craniofacial, cardiac, thymic and central nervous system defects.[3] They found a relative risk of 26 for this group of major congenital malformations after systemic isotretinoin exposure during some parts of the first 10 weeks after conception.[3] Elective termination of pregnancy (ETOP) was decided in more than 50% of exposed pregnancies and 20% of the remaining pregnancies ended in a first trimester spontaneous abortion.[3] Reports of congenital anomalies after isotretinoin use accumulated and consequently, in 1988 the marketing authorisation holder of isotretinoin implemented a world-wide Pregnancy Prevention Programme (PPP) to better prevent pregnancies among systemic isotretinoin users.[4] The PPP included an educational programme for prescribers and patients including material to be used in counselling women about the need to prevent pregnancy while taking isotretinoin. Conditions for prescribing included a negative pregnancy test, the use of reliable contraception and a signed patient consent form.[4] In 2003, a review of isotretinoin by the European Medicine Agency (EMA) resulted in a compulsory European harmonised PPP for all isotretinoin containing products.[1] The elements of the European wide PPP are listed in box 1.

Box 1: Elements of the European Union isotretinoin pregnancy prevention programme

1. Isotretinoin is contraindicated in pregnant women and should only be initiated in women of reproductive age who understand the teratogenic risk and the need for regular follow-up.
2. Use of effective contraceptive measures from 4 weeks before isotretinoin initiation until 4 weeks after treatment discontinuation. At least one and preferably two complementary forms of contraception including a barrier method should be used.
3. Pregnancy testing should be performed before, during and 5 weeks after discontinuation of isotretinoin.
4. Isotretinoin should only be prescribed by or under the supervision of a physician with experience in the use of systemic retinoids.
5. Prescription should be limited to 30 days of treatment and continuation of treatment requires a new prescription.
6. Dispensing of isotretinoin should occur within a maximum of 7 days after prescription.
7. Educational programmes for healthcare professionals including prescribers and pharmacists, and patients are in place to inform them about the teratogenic risk and to create awareness of the pregnancy prevention programme.

The safe use of isotretinoin in women of reproductive age is in the interest of public health because of the potential risk of spontaneous and elective abortions, and, more importantly, children with major congenital anomalies require continuous healthcare throughout their life. Although a PPP has been implemented in the EU, pregnancies during isotretinoin therapy still occur.[5, 6] The regulatory authorities of 16 EU member states responded in 2009 to a survey that isotretinoin exposed pregnancies have occurred in their country.[7] A French study between 2003 and 2006 estimated a pregnancy rate from 0.4 to 1.2 / 1000 female isotretinoin users within reproductive age.[6] Studies in the Netherlands observed that only 52 – 59% of the female isotretinoin users of reproductive age used concomitant hormonal contraceptives, which was higher than the 39 – 46% observed in the general female population of similar age, but lower than anticipated.[8, 9] Although these studies show limited compliance with the

isotretinoin PPP, it is not known whether isotretinoin exposure also occurs during pregnancy and what the outcome of these pregnancies is. Therefore, the objective of our study was to estimate isotretinoin exposure in Dutch pregnant women despite the implemented PPP and second, to analyse the occurrence of adverse fetal and neonatal outcomes in these isotretinoin exposed pregnancies.

METHODS

Data sources

For this population-based study a cohort of 203,962 pregnancies consisting of 208,161 fetuses was constructed using a linkage between the PHARMO Database Network and the Netherlands Perinatal Registry (PRN). The PHARMO Database Network is a dynamic population-based cohort including, among other information, drug-dispensing records from community pharmacies for more than 3 million individuals in the Netherlands (approximately 20% of the Dutch population) that are collected since 1986.[10] The drug dispensing data contain the following information per prescription: the Anatomical Therapeutic Chemical (ATC) classification of the drug, dispensing date, regimen, quantity dispensed and estimated length of duration of use.[11] The PRN is a nationwide registry that contains linked and validated data from four databases: the national obstetric database for midwives (LVR-1), the national obstetric database for gynaecologists (LVR-2), the national obstetric database for general practitioners (LVR-h) and the national neonatal/paediatric database (LNR).[12] The registry contains information about care before, during and after delivery as well as maternal and neonatal characteristics and outcome of 95% of 180,000 pregnancies annually in the Netherlands with a gestational age of at least 16 weeks. The PRN includes information on pregnancy outcome including congenital anomalies detected during pregnancy, at birth or within the first year after birth. The probabilistic linking method between PHARMO and PRN has been described in detail elsewhere but was generally based on the birth date of the mother and child and their postal zip codes.[13] To be included in the cohort the mother should be registered in the community pharmacy database of PHARMO during the whole pregnancy. The date of conception was estimated based on the last menstrual period or ultrasound, as recorded in the PRN, and was truncated to full weeks.

Isotretinoin dispensings

All dispensings for systemic (oral) isotretinoin (ATC D10BA01) filled in community pharmacies by women included in our cohort within the 12 months period before or during pregnancy were extracted from the PHARMO Database Network. Considering a daily dosage of 0.5 – 1 mg / kg daily,[1] isotretinoin prescriptions dispensed on the same day were assumed to be used simultaneously and therefore these dispensings were pooled and considered as one dispensing (e.g., the prescriptions of 10 mg and 20 mg tablets dispensed at the same time to reach a daily dosage of 30 mg). For each isotretinoin dispensing, the length of the dispensing was calculated by dividing the total number of prescribed units by the number of units (doses) to be taken per day. In case isotretinoin dispensings that were pooled together had different lengths, the length of the single dispensing with the longest duration was used. To assess compliance with the PPP, we calculated the proportion of dispensings that exceeded 30 days, which is the maximum length according to the EU PPP.

Drug exposure interval

For all pregnancies (N=203,962) with gestational age of at least 16 weeks included in the cohort, isotretinoin exposure was estimated based on isotretinoin dispensing data (ATC D10BA01) filled by the mother during the 12 months period before and during pregnancy. Exposure in person time (days)

was calculated by dividing the total number of prescribed units by the number of prescribed units per day. Isotretinoin exposure periods were defined considering a possible overlap of isotretinoin dispensings. Gaps, isotretinoin free periods between two isotretinoin dispensings, were not permitted meaning that an isotretinoin exposure period ends once an isotretinoin free period was identified. Using the start and end date of the isotretinoin exposure period, the number of days exposed was estimated for the following exposure intervals: 30 days before conception, first 90 days of gestation (first trimester), day 90 – 179 of gestation (second trimester) and day 180 – delivery (third trimester). In addition, the entire period 30 days before pregnancy until delivery as well as the period from 30 days before till the end of the first trimester were analysed separately.

Adverse fetal or neonatal outcomes

For each fetus (N=208,161), we determined whether adverse fetal or neonatal outcomes were reported. Adverse fetal or neonatal outcomes were defined as all intrauterine deaths ≥ 16 week of gestation and liveborn infants with major congenital anomalies. If possible, congenital anomalies were categorised into nine subgroups: abdominal wall and skin disorders; cardiovascular defects; defects in the digestive system; defects in the nervous system; musculoskeletal defects; respiratory defects; urogenital defects; multiple, syndrome or chromosomal anomalies; or other congenital malformations. As we were interested in adverse fetal outcomes potentially induced by maternal drug exposure, chromosomal anomalies were not considered as an adverse outcome in the analyses.

Analysis

Potential exposure to isotretinoin in the 30 days before or during pregnancy was calculated per 10,000 pregnancies for the aforementioned exposure intervals including their 95% confidence intervals (95% CIs). The proportions of adverse fetal outcome among isotretinoin exposed and unexposed fetuses or neonates were calculated including their 95% CIs. We used multiple logistic regression models to calculate odds ratios (ORs) and 95% CIs to estimate associations between adverse fetal or neonatal outcome and maternal isotretinoin exposure. We adjusted for maternal age at conception (<20, 20-24, 25-29, 30-34, ≥35), and if possible also for calendar time (year of conception) and gender of the infant. Analyses for specific congenital anomalies were performed when > 3 cases were observed. The t test or Fisher exact test was used to derive *p*-values when comparing continuous or categorical variables between study groups. Statistical significance was assumed for two-sided *p*-values <0.05. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina, US).

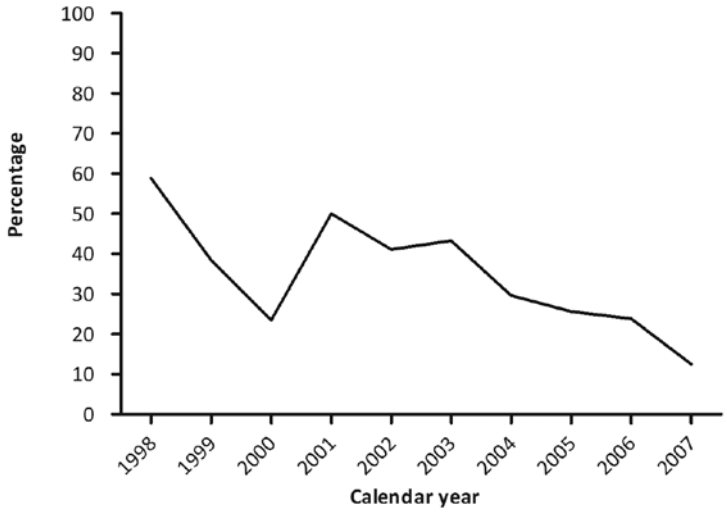
RESULTS

Between 1 January 1999 and 1 September 2007 in the Netherlands, a total of 203,962 pregnancies corresponding to 208,161 fetuses (including multiple births) were included in our study. The mean maternal age at conception was 30.3 years (SD 4.6) and mean duration of pregnancy was 39 weeks and 3 days (SD 19 days).

Isotretinoin dispensings

A total of 416 isotretinoin dispensings to 130 of the 203,962 women in the 12 months period before or during pregnancy were identified. In 139 of the 416 isotretinoin dispensings (33.4%), the dispensing consisted of > 30 days of isotretinoin use. Figure 1 shows that the percentage of isotretinoin dispensings in the year before or during pregnancy exceeding the maximum duration of 30 days decreased over calendar time from 50% in 2001 to 13% in 2007.

Figure 1: Percentage of isotretinoin dispensing exceeding the maximum duration of 30 days by calendar year



Isotretinoin exposed pregnancies

Demographics for isotretinoin exposed and unexposed pregnancies are presented in Table 1.

Table 1: Description of the study population

	Isotretinoin exposed*	Isotretinoin unexposed	*p*-value
Pregnancies (N=203,962)	51	203,911	
Mean (±SD) maternal age at conception in years (95% CI)	29.1 (4.9) (27.8 – 30.5)	30.3 (4.7) (30.3 – 30.3)	0.56
Mean (±SD) gestational age at delivery in weeks (95% CI)	39 (25 days) (38 – 40)	39, 3 days (19 days) (39, 3 days – 39, 3 days)	0.33
Fetuses (N=208,161)	53	208,108	
Gender (boy %)	47.2% (33.3 – 61.1)	51.5% (51.3 – 51.7)	0.53
Maternal age at conception in years, N, column %			0.37
< 20	2 (3.8%)	4,063 (2.0%)	
≥ 20 - 25	7 (13.2%)	22,144 (10.6%)	
≥ 25 - 30	21 (39.6%)	68,366 (32.9%)	
≥ 30 - 35	14 (26.4%)	81,581 (39.2%)	
≥ 35	9 (17.0%)	31,951 (15.4%)	
Gestational age at delivery in weeks, N, column %.			0.64
< 27	1 (1.9%)	2,198 (1.1%)	
27 - 30	1 (1.9%)	1,167 (0.6%)	
31 - 33	0 (0.0%)	2,008 (1.0%)	
34 - 36	3 (5.7%)	7,126 (3.4%)	
37 - 39	12 (22.6%)	50,854 (24.4%)	
> 39	36 (67.9%)	144,755 (69.5%)	
Adverse fetal outcome, N; % (95% CI)	5; 9.4% (1.3 – 17.6)	9,041; 4.3% (4.3 – 4.4)	0.08

CI=Confidence interval
**In the 30 days before conception or during pregnancy*

Overall, 51 pregnancies, 2.5 (95% CI 1.9 – 3.3) per 10,000 pregnancies, were potentially exposed to isotretinoin in the 30 days before conception or during pregnancy, despite the implemented PPP. Forty-five pregnant women, 2.2 (95% CI 1.6 – 2.9) per 10,000 pregnancies, were estimated to be exposed to isotretinoin during pregnancy of whom 27 (60%) started isotretinoin treatment while already being pregnant. In 18 pregnancies (40%), the conception occurred during isotretinoin treatment. Six pregnancies were identified within 1 month after isotretinoin discontinuation and were estimated to be exposed only before conception. In 40 out of 203,962 pregnancies, 2.0 (95% CI 1.4 – 2.6) per 10,000 pregnancies, an isotretinoin prescription was filled during pregnancy and 32 pregnancies, 1.6 (95% CI 1.1 – 2.2) per 10,000 pregnancies, received isotretinoin more than once during pregnancy. The number of isotretinoin dispensings per pregnancy ranged from 1 to 7, with a median of 2.5. The estimated isotretinoin exposure per exposure interval is presented in Table 2.

Table 2: Potential isotretinoin exposed pregnancies per exposure interval

Isotretinoin exposure interval*	Exposed pregnancies (N=203,962)	Exposed pregnancies per 10,000 pregnancies (95% CI)	Median number of days exposed per pregnancy (range)
30 days before conception (30 days period)	23	1.1 (0.7 – 1.7)	24 (3 – 30)
1st trimester (90 days period)	28	1.4 (0.9 – 2.0)	31 (3 – 88)
2nd trimester (90 days period)	25	1.2 (0.8 – 1.8)	57 (1 – 90)
3rd trimester (90-103 days period)	26	1.3 (0.9 – 1.8)	62 (1 – 103)
During pregnancy (270 days period)	45	2.2 (1.6 – 2.9)	63 (3 – 236)
30 days before or during pregnancy (300 days period)	51	2.5 (1.9 – 3.3)	63 (7 – 236)
30 days before or during 1st trimester (120 days period)	35	1.7 (1.2 – 2.4)	32 (7 – 114)

CI=Confidence interval
**Categories are not mutually exclusive but indicate the number of pregnancies exposed to isotretinoin during that exposure interval*

Among the pregnancies estimated to be exposed to isotretinoin during pregnancy (N=45), the number of exposed days during pregnancy ranged from 3 to 236 days with a median of 63 days. Figure 2 shows that the number of women estimated to be exposed to isotretinoin during pregnancy was the highest in 2006 with 3.5 pregnancies (95% CI 1.7 – 6.4) per 10,000 pregnancies.

Adverse fetal or neonatal outcomes

Independent of isotretinoin exposure, adverse fetal or neonatal outcomes were observed for 9,046 of the 208,161 fetuses (4.4% (95% CI 4.3 % – 4.4%)). The 51 pregnancies potentially exposed to isotretinoin in 30 days before conception or during pregnancy corresponded to 53 fetuses or neonates including two multiple births. Five of these, all singletons, had an adverse fetal or neonatal outcome (9.4% (95% CI 3.5% – 19.7%)). These included three intrauterine deaths and two liveborn infants with major congenital anomalies (see Table 3). Among those potentially exposed during pregnancy only (N=47), 6.4% (95% CI 1.7% – 16.4%) had an adverse fetal or neonatal outcome. The OR for adverse fetal or neonatal outcome after potential isotretinoin exposure in the 30 days before or during pregnancy was 2.3 (95% CI 0.9 – 5.7) after adjustment for maternal age (see Table 3). Restricting the analysis to

the potential isotretinoin exposure during pregnancy, the adjusted OR of an adverse fetal outcome was 1.5 (95% CI 0.5 – 4.8). The number of cases was too low to allow for adjustments in addition to maternal age. The adjusted OR of any fetal or neonatal outcome was significantly increased at 3.6 (95% CI 1.4 – 9.4) for isotretinoin exposure during the 30 days before or first trimester of pregnancy.

Figure 2: Isotretinoin exposed pregnancies per 10,000 pregnancies by calendar year

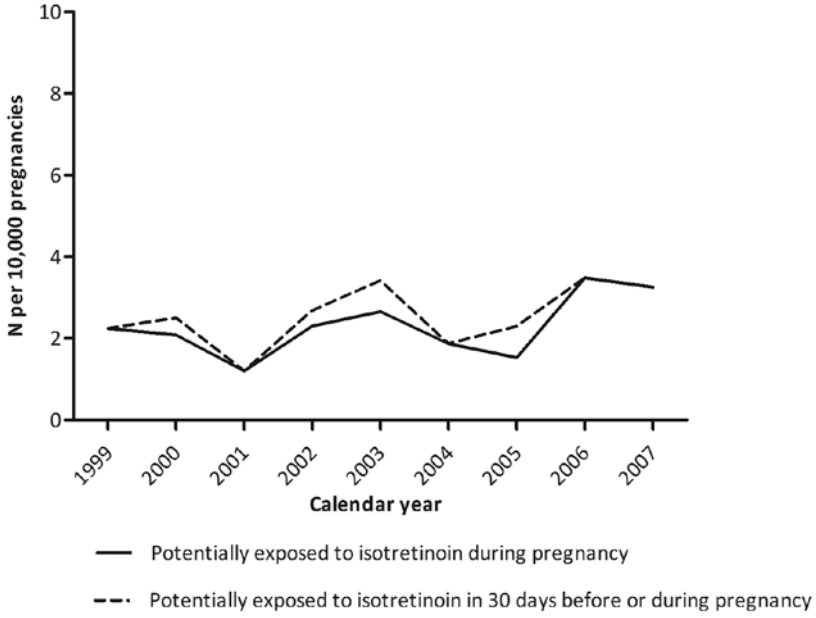


Table 3: Odds ratios for adverse fetal and neonatal outcomes and isotretinoin exposure in 30 days before or during pregnancy

Isotretinoin exposed fetuses	Exposed fetuses with adverse outcomes	OR (95% CI)	Adjusted OR* (95% CI)
30 days before conception	3†	1.5	1.5
During pregnancy (N=47)		(0.5 – 4.8)	(0.5 – 4.8)
30 days before or during pregnancy (N=53)	5†‡	2.3	2.3
		(0.9 – 5.8)	(0.9 – 5.7)
30 days before or 1st trimester (N=35)	5†‡	3.7	3.6
		(1.4 – 9.5)	(1.4 – 9.4)

CI=confidence interval

**maternal age in categories (<20, 20-24, 25-29, 30-34, ≥35)*

† Includes three intrauterine deaths

1) in week 19, potentially exposed first 29 days following conception.

2) in week 35, potentially exposed 10 weeks following conception and from week 18 until week 32.

3) in week 38, also reported an unspecified septal defect; potentially exposed first 8 days following conception, during week 12 until week 24 and during week 28 until week 38.

‡ Includes two liveborn infants with major congenital anomalies.

1) Neural tube defect, potentially exposed all 30 days before conception, not after conception.

2) Major congenital anomaly not further specified, potentially exposed the first 15 days of the 30 days before conception, not after conception.

DISCUSSION

This study shows that 2 per 10,000 pregnancies were exposed to isotretinoin despite the PPP which is implemented to prevent isotretinoin use during pregnancy. Although this study was not intended to estimate the teratogenic risks of isotretinoin, adverse fetal and neonatal outcomes potentially related to isotretinoin exposure were observed. That there are still women who are using isotretinoin during pregnancy despite the implementation of the PPP is of major concern. Especially since the majority of isotretinoin exposed women (60%) were already pregnant at the time of first isotretinoin prescription and it seems that pregnancy was not always excluded before isotretinoin dispensing (box 1). These exposed pregnancies could probably have been prevented when appropriate pregnancy testing would have been performed. Furthermore, it was earlier demonstrated that women of reproductive age treated with isotretinoin did not always use effective contraceptive measures because only up to 59% of these women concomitantly used hormonal contraceptives.[8, 9] Limited compliance with the PPP was also observed in a survey among Dutch pharmacists which indicated that in 2007 and 2011, 44% and 49% of pharmacists, respectively, checked the use of contraception at every isotretinoin dispensing.[14] The percentage of pharmacists that asked for negative pregnancy tests was stable with 15% and 16%, respectively and is in line with our study which demonstrated that pregnancy is not always excluded before initiating isotretinoin and result in isotretinoin exposed pregnancies that could have been prevented. Our study showed that compliance with the recommended maximum length of prescription of 30 days was limited since one-third of isotretinoin dispensings exceeded 30 days which however decreased from 50% in 1999 to 13% in 2007. Based on these results it is clear that compliance with the PPP in the Netherlands between 1999 and 2007 was incomplete. These findings suggest an ongoing need to educate healthcare professionals and patients on the fetal risks of isotretinoin and the PPP, especially since isotretinoin is mostly used in young women of reproductive age.

Previous studies on isotretinoin use during pregnancy in other Western countries showed comparable results indicating that limited compliance to the PPP is not restricted to the Netherlands.[6, 15-17] In the United States (US), the most recent isotretinoin PPP, called iPLEDGE, has been implemented since 2006 and is stricter than the EU PPP. iPLEDGE is an internet-based system that requires registration of all stakeholders with monthly updates on prescription, pregnancy tests, contraceptive use and acknowledgement of risks.[17] The pregnancy rate among isotretinoin users in the US with the iPLEDGE PPP was estimated at 2.7 / 1,000 treatment courses and did not change compared to the previous PPP called SMART (System to Manage Accutane-Related Teratogenicity) while only small improvements in compliance with contraceptive measures were observed.[17, 18] Apparently, also iPLEDGE does not bring complete security because further restrictive measures as in iPLEDGE do not seem to improve the results and may add unnecessary burden to the healthcare system since healthcare professionals and patients need to register and verify information on a monthly basis.[4]

Strengths and weaknesses of the study

A strength of this study is that we used a population-based design including virtually complete and detailed drug dispensing data and pregnancy outcome data of a large cohort, which enabled estimating nationwide isotretinoin exposure rates among pregnant women. A known limitation of using drug dispensing data is that it does not confirm the actual use of the drug under study and does not provide information on the precise time window of drug use. In addition, it is likely that women may change or stop their medication use when they become aware of pregnancy. However, it should be noted that our data show that the majority (80%) of pregnant women who filled prescriptions for isotretinoin came back for refills, suggesting that they really used the drug.

This study provides no information on spontaneous abortions that occurred until gestational age of 16 weeks and ETOPs because these data are not captured in the PRN database and these pregnancies were thus not included in our cohort. This resulted in an underestimation of the number of pregnancies that were potentially exposed to isotretinoin in the 30 days before or during pregnancy and the adverse fetal and neonatal outcomes. Studies that estimated the teratogenic risk of isotretinoin using prospectively documented isotretinoin exposed pregnancies found much higher proportions of pregnancies resulting in spontaneous abortion, stillbirth or reported congenital malformations, that is, 36% (13 of the 36 fetuses)[3] and 26% (6 of the 23 fetuses)[5].

Without detailed information on drug exposure preferably verified by the patient whether the drug was actually taken and detailed descriptions of the diagnosed fetal outcome as well as on spontaneous abortions, the teratogenic risk of isotretinoin could not be accurately estimated. With regard to the adverse fetal outcomes observed in our study, we cannot exclude that they had any other aetiology than isotretinoin exposure. Owing to the low number of cases it was also not possible to adjust in the statistical analysis for important confounding factors other than maternal age such as smoking, alcohol intake, previous pregnancy outcomes and exposure to other potentially teratogenic drugs. Detection bias may also have influenced the incidence and estimated risks of congenital anomalies since more detailed diagnostics might have been used in pregnancies exposed to isotretinoin compared to the unexposed pregnancies. Nevertheless, the results of our study are in line with the undisputed embryotoxicity of isotretinoin and suggestive of an increased risks of adverse fetal or neonatal events when isotretinoin is dispensed for use in the 30 days period before or during pregnancy.

Implications and future research

In the Netherlands, approximately 180,000 pregnancies are reported annually.[19] When extrapolating the 2.2 (95% CI 1.6 – 2.9) per 10,000 women potentially exposed to isotretinoin during pregnancy to a national level, there would be 29 to 52 isotretinoin-exposed pregnancies per year yielding unnecessary risks for congenital anomalies and fetal deaths. Therefore, it is in the interest of public health to implement effective PPPs and improve these measures or their compliance as much as possible to reduce isotretinoin use during pregnancy to the lowest possible level.

With the present study only the period 1999 to 2007 has been evaluated. The past years in the Netherlands, the PPP is communicated to healthcare professionals via product information,[20] national general practitioner standards on treatment of acne,[21] drug prescription and dispensing systems,[22] the website of the Dutch Medicines Evaluation Board[23] and the common (national) literature on drug information.[24] Furthermore, research on isotretinoin use in the Netherlands and the PPP is conducted and published in (inter)national scientific medical journals.[7-9, 14, 25-28] Consequently, data after 2007 are needed to judge if attention for the isotretinoin PPP during recent years has improved the carefulness with which isotretinoin is prescribed and dispensed.

Conclusions

Although a PPP was implemented almost 15 years ago, we showed that there are still pregnancies exposed to isotretinoin in the Netherlands which could have been prevented if appropriate exclusion of pregnancy before isotretinoin initiation would have been performed. These findings from the Netherlands add to the evidence that there is no full compliance to the isotretinoin PPP in many Western countries. Given the limited success of iPLEDGE, the question is which further measures are able to improve compliance.

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8

DISPENSING OF POTENTIALLY TERATOGENIC DRUGS BEFORE CONCEPTION AND DURING PREGNANCY: A POPULATION BASED STUDY

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ABSTRACT

Objective To study the dispensing of potentially teratogenic drugs in the 12-month period before as well as during pregnancy in the Netherlands.

Design Population-based study.

Setting A cohort was constructed using a linkage between the PHARMO Database Network and the Netherlands Perinatal Registry (PRN).

Population A total of 203,962 Dutch pregnancies reported between 1999 and 2007.

Methods Drug dispensing information was identified from the PHARMO Database Network for the 12-month period before conception and during pregnancy. Drugs with either a Swedish FASS 'D' classification, an Australian ADEC or American FDA 'D' or 'X' classification were considered potentially teratogenic (n=202).

Mean outcome measures Proportion of pregnancies that received potentially teratogenic drugs in the 12-month period before and during pregnancy and specific for the risk category X drugs and newly initiated drugs.

Results Sixteen percent of the pregnancies received a potentially teratogenic drug in the 12-month period before and 5.07% during pregnancy. Doxycycline and paroxetine were most frequently received during pregnancy by 1.01% and 0.85% of women, respectively; 0.66% of the women received a risk category X drug during pregnancy which most frequently consisted of triptorelin (0.25%), norethisterone (0.22%), and simvastatin (0.03%). Fifty-tree percent of the women who received a potentially teratogenic drug during pregnancy received this for the first time during the study period. These percentages were heterogeneous between therapeutic drug classes.

Conclusions Five percent of the pregnancies received a potentially teratogenic drug during pregnancy and 0.66% a drug from the risk category X. It may be possible to reduce these proportions in future when reasons for prescription have been explored.

INTRODUCTION

At the moment of first marketing, the safety of drugs during pregnancy is often not established since pregnant women are generally excluded from clinical studies. Vigilant monitoring during the post-marketing period is important to gain more and better knowledge on the possible risks for the developing embryo or fetus after maternal drug exposure. Despite the limited information on the effects of drugs on embryonic or fetal health, prescription drugs (excluding vitamins and minerals) are used in 27 – 93% of the pregnancies in developed countries.[1] Even though for some drugs contraindications or warnings on drug use during pregnancy are in place, in pregnant women with certain medical conditions such as epilepsy or depression the expected treatment benefits may outweigh the possible harms. Furthermore, it cannot be completely avoided as a large proportion of pregnancies in Western Europe is unintended (42%).[2] Nevertheless, unnecessary or inappropriate drug use during pregnancy should be avoided, especially teratogenic drugs. Teratogenic drugs, when used shortly before or during pregnancy, can irreversibly modify growth, structure, or function of the developing embryo or fetus, resulting in potential spontaneous abortion, premature delivery and mental and physical disabilities.[3]

Various studies identified concerns on the use of drugs with a teratogenic potential. Less than half (42%) of women of reproductive age using drugs with a teratogenic potential used concomitant contraceptives in the Netherlands and comparable results were observed in the United States (US).[4-6] Previous study in the US, Canada and Ireland showed that 4.2 – 7.8% of pregnant women received potentially teratogenic drugs.[1, 7-11] In the Netherlands, in the period between 1994 and 2003, 1.1% of all drugs received during pregnancy were potentially harmful for the embryo/fetus.[12] In view of the possible impact on public health, it is important to further explore the use of potentially teratogenic drugs among pregnant women in the Netherlands. In this population-based study, we examined the dispensing patterns of potentially teratogenic drugs to Dutch women in the year before and during pregnancy in the period between 1999 and 2007.

METHODS

Data sources

For this population-based study, a cohort of 203,962 Dutch pregnancies was identified using a linkage between the PHARMO Database Network and the Netherlands Perinatal Registry (PRN) reported between 1 January 1999 and 31 September 2007, which correspond to 18% of all pregnancies included in the PRN during this period. The PHARMO Database Network is a dynamic cohort of participants that includes, among other information, drug-dispensing records from community pharmacies for more than three million individuals in the Netherlands (approximately 20% of the Dutch population) collected since 1991.[13] The drug dispensing data contain the following information per prescription: the Anatomical Therapeutic Chemical (ATC) classification of the drug, dispensing date, regimen, quantity dispensed, and estimated length of duration of use.[14] The PRN is a nationwide registry that contains linked and validated data from four databases: the national obstetric database for midwives (LVR-1), the national obstetric database for gynaecologists (LVR-2), the national obstetric database for general practitioners (LVR-h) and the national neonatal/paediatric database (LNR).[15] The registry contains information about care before, during, and after delivery as well as maternal and neonatal characteristics and outcome of 95% of 180,000 pregnancies annually in the Netherlands with a gestational age of at least 16 weeks. The linking method between PHARMO and PRN has been described elsewhere but was generally based on the birth date of the mother and child and

their addresses using postal zip codes.[16] To be able to define drug dispensing in the 12-month period before conception and during pregnancy, women needed to be registered in the community pharmacy database of the PHARMO Database Network for the complete study period, i.e. 12-month period before conception and during pregnancy. The unit of analysis was an individual pregnancy.

Drugs of interest

The outpatient drug dispensing during the 12-month period before conception until the end of pregnancy was extracted from the PHARMO Database Network for all subjects included in our cohort. Potentially teratogenic drugs were selected using the classification systems of the US Food and Drug Administration (FDA), the former Australian Drug Evaluation Committee (ADEC) and the Swedish Catalogue of Approved Drugs (FASS).[17-19] These classifications consist of four or five categories (A, B, C, D, X) and several subcategories to categorise the teratogenic potential of drugs (see Appendix I). The FDA category D includes drugs for which there is positive evidence of fetal risks, but the benefits may be acceptable despite the risks; category X drugs are considered contraindicated for use in pregnancy because of evidence on fetal risk from studies in animals or humans, or based on human experience. Drugs for which risks in pregnancy have not been established but for which there is no benefit may be classified as category X.[20] In general, we selected the drugs with either a FASS 'D' classification or an ADEC or FDA 'D' or 'X' classification resulting in 202 potentially teratogenic drugs. The drugs of interest are coded according to ATC code and are listed in Appendix II. The method of identification of potentially teratogenic drugs has been previously described.[4] The drugs were divided into eleven mutually exclusive categories based on therapeutic indication: anti-infective & anti-parasitic agents, agents acting on the renin-angiotensin-system (RAS), anti-thrombotic agents, statins, dermatologicals, pituitary, hypothalamic and sex hormones, anti-neoplastic agents, immunomodulating agents, anti-epileptics agents, psycholeptic and psychoanaleptic agents and last, miscellaneous agents. Separate analyses were performed for the 39 category X drugs according to either ADEC or FDA classification. Reproductive hormonal drugs (ATC G03 and H01C) including androgens, estrogens, progestogens and gonadotropins as well as the gonadotropin releasing hormone (GrNH) agonists (ATC L02AE02 and L02AE04) were excluded from some analyses as these drugs may be dispensed to women to stimulate ovulation or used for *in vitro* fertilisation (IVF). The seven drugs with a mandatory pregnancy prevention programme in the Netherlands were analysed separately: thalidomide (L04AX02), lenalidomide (L04AX04), isotretinoin (D10BA01), acitretin (D05BB02), alitretinoin (L01XX22), bosentan (C02KX01) and ambrisentan (C02KX02). In the European Union (EU), alitretinoin (D11AH04) has been licensed to treat severe chronic hand eczema since April 2009, and is therefore not considered in this study.

Drug exposure periods

The dispensing of potentially teratogenic drugs was examined for the 12-month period before conception until end of pregnancy. We identified seven drug exposure periods with a duration of 3 months each i.e. 12 – 9 months before pregnancy, 9 – 6 months before pregnancy, 6 – 3 months before pregnancy, 3 months before pregnancy, first trimester of pregnancy (day 1 until day 90), second trimester of pregnancy (day 91 until day 180), and third trimester of pregnancy (day 181 until delivery). The start of pregnancy was based on the last menstrual period or ultrasound, as recorded in the PRN database and truncated to full weeks.

Analysis

Per 3-month period, we counted the number of pregnancies that received drugs of interest. Dispensing

rates per 1000 pregnancies and the 95% confidence intervals (95% CI) around them were calculated by dividing the number of pregnancies during which a potentially teratogenic drug was filled by the total number of pregnancies included in our study. This was done per 3-month period for all teratogenic drugs, drug categories and category X drugs according to ADEC or FDA classification system and 95% CI were calculated. Dispensings were only counted in the 3-month period in which they were dispensed. A sensitivity analysis was performed to account for possible misclassification of drug use during pregnancy. We calculated the duration and end date of the dispensing for drugs initially dispensed before conception. When the end date occurred after the conception date we also counted the dispensing during pregnancy. Analyses restricted to newly initiated drugs were performed to assess the initiation of potentially teratogenic drugs during the study period. A drug dispensing was considered a newly initiated drug if the particular women did not receive that drug earlier in the 12-month period before or during pregnancy. Descriptive statistics were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina, US).

RESULTS

A total of 203,962 pregnancies in the Netherlands between 1 January 1999 and 1 September 2007 were included in our study. The mean maternal age at conception was 30.33 years (SD 4.65) and mean duration of pregnancy was 39 weeks and 3 days (SD 19 days). Demographics of the pregnancies are presented in Table 1.

During 156,389 of the 203,962 pregnancies (76.68%) any prescription drug was filled within the 12-month period before conception and 137,155 women (67.25%) received any prescription drug during pregnancy. Potentially teratogenic drugs were dispensed to 31,996 pregnant women (15.69%) in the year before conception and to 10,343 women (5.07%) during pregnancy (Table 2). As visualised in Figure 1, the proportion of pregnant women who received a potentially teratogenic drug decreased after conception. In 7.09% of the pregnancies a potentially teratogenic drugs was filled within 3 months before pregnancy; in the first, second and last trimester, percentages decreased to 3.72%, 1.59% and 1.65%, respectively. Excluding reproductive hormones, ovulation stimulants and other fertility drugs, in the 12-month period before conception 22,805 pregnancies (11.18%) received a potentially teratogenic drug and 6,921 (3.39%) received it during pregnancy. Furthermore, the peak during the 3-months period before pregnancy – observed when these drugs were included – disappeared. A similar pattern was observed for category X drugs, which 7,159 women (3.51%) received in the 12-month period before conception and 1,350 women (0.66%) received during pregnancy. After excluding reproductive hormones, ovulation stimulants and other fertility drugs these numbers decreased to 952 pregnancies (0.47%) and 268 pregnancies (0.13%), respectively.

Table 1: Demographics and characteristics of pregnancies included in the PHARMO-PRN cohort

	Pregnancies (n=203,962)
Pregnancies that received drugs during pregnancy (n; %, 95% CI)	
Pregnancies that received no prescription drugs	66,807; 32.8% (32.5 – 33.0)
Pregnancies that received a prescription drug	137,155; 67.3% (67.0 – 67.4)
Pregnancies that received a potentially teratogenic drug	10,343; 5.1% (5.0 – 5.2)
Pregnancies that received a category X drug	1,350; 0.7% (0.6 – 0.7)
Maternal age at conception in years (Mean (±SD))	30.33 (4.65)
Overall	30.45 (4.42)
Pregnancies that received no prescription drugs*	30.27 (4.76)
Pregnancies that received a prescription drug *	31.22 (4.84)
Pregnancies that received a potentially teratogenic drug *	31.81 (4.85)
Pregnancies that received a category X drug *	
Duration of pregnancy (Mean (±SD))	
Overall	39 weeks, 3 days (19 days)
Pregnancies that received no prescription drugs *	39 weeks, 3 days (19 days)
Pregnancies that received a prescription drug *	39 weeks, 3 days (18 days)
Pregnancies that received a potentially teratogenic drug *	39 weeks, 0 day (21 days)
Pregnancies that received a category X drug *	38 weeks, 6 days (24 days)
Year of conception	
1999	17,834
2000	23,981
2001	24,871
2002	26,073
2003	26,354
2004	26,775
2005	26,097
2006	25,837
2007	6,140

** During pregnancy; SD=standard deviation. CI=confidence interval.*

Figure 1: Pregnancies that received a potentially teratogenic drug or a category X drug per 1000 pregnancies

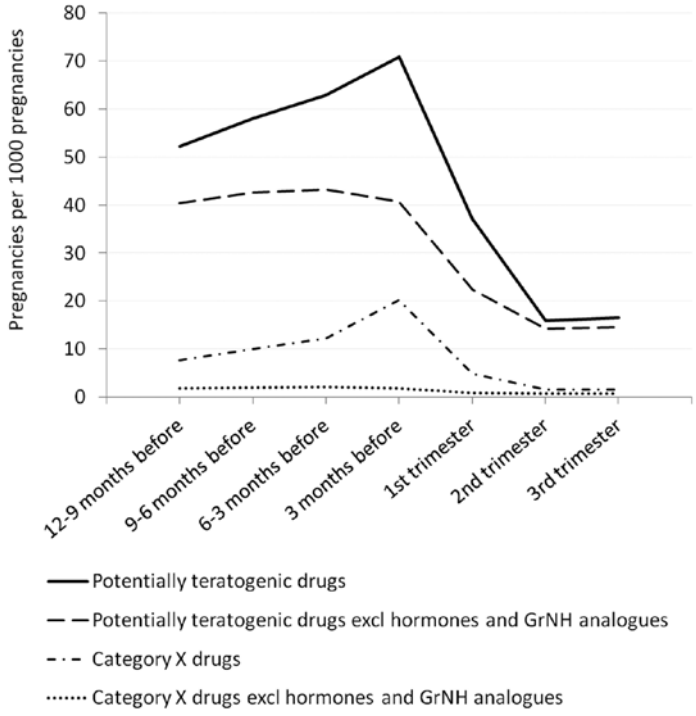
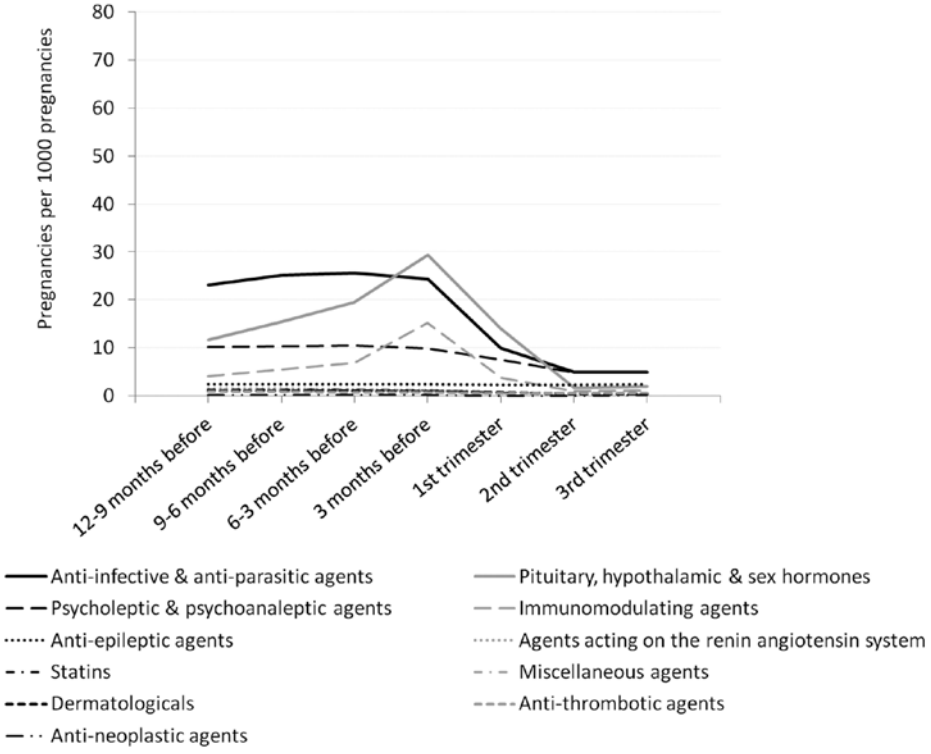


Figure 2: Pregnancies that received a potentially teratogenic drug per drug category per 1000 pregnancies



Drug categories

Within the 12-month period before conception, pregnant women most frequently received a potentially teratogenic drug classified as 'anti-infective and anti-parasitic agents' (8.30% of the pregnancies), followed by 'pituitary, hypothalamic and sex hormones' (5.12%), 'immunomodulating agents' (1.91%) and 'psycholeptic and psychoanaleptic agents' (1.78%). During pregnancy these percentages decreased: 'anti-infective and anti-parasitic agents' (1.78%), 'pituitary, hypothalamic and sex hormones' (1.65%), 'psycholeptic & psychoanaleptic agents' (0.91%) and 'immunomodulating agents' (0.44%). Figure 2 presents the number of pregnant women who received a potentially teratogenic drug per drug class and per period of interest. Except for the 'anti-epileptics' and 'anti-neoplastics' included in our study, fewer potentially teratogenic drugs were received during pregnancy as compared with the period before pregnancy.

Individual drugs

Of the 202 potentially teratogenic drugs, 100 were dispensed at least once in the 12-month period before or during pregnancy and 92 were received during pregnancy. Information for the 20 potentially teratogenic drugs most frequently received during pregnancy is provided in Table 2. Doxycycline and paroxetine were most frequently received in the 12-month period before conception (by 54.51 and 17.25 pregnancies per 1000 pregnancies, respectively) as well as during pregnancy (by 10.08 and 8.54 pregnancies per 1000 pregnancies, respectively). Figure 3 shows that the number of pregnancies per 1000 pregnant women who received potentially teratogenic drugs declined after conception, except for carbamazepine, which remained stable over the complete study period. Peaks in the 3-month period before conception were observed for 28 potentially teratogenic drugs including five of the ten most frequently received drugs, i.e. triptorelin, progesterone, follitropin α , medrogestron – IM, norethisterone. The category X drugs most frequently received during pregnancy are presented in Table 3 and included triptorelin (2.49 per 1000 pregnancies), norethisterone (2.17 per 1000 pregnancies) and simvastatin (0.31 per 1000 pregnancies).

With regard to the drugs with a pregnancy prevention programme, isotretinoin was dispensed to 101 pregnant women (0.50 per 1000 pregnancies) before conception, of whom 26 received the drug in the 3-month period before pregnancy. Forty pregnancies (46 in the sensitivity analysis) received isotretinoin during pregnancy i.e. 20 in the first trimester, 20 in the second trimester and 26 in the third trimester. Thirty-three of the 40 pregnant women received isotretinoin more than once during pregnancy. Acitretin was dispensed to six pregnancies in the 12-month period before conception and four received acitretin during pregnancy. We did not identify pregnant women who received ambristentan, bosentan, thalidomide, lenalidomide and alitretinoin during the study period.

Sensitivity analysis

In the sensitivity analysis the percentage of pregnant women who received potentially teratogenic increased from 5.07% to 6.14% when including pregnancies with a dispensing before conception with a duration of use extending beyond conception date. For category X drugs the percentage increased from 0.66% to 1.19%. As presented in Table 3, similar patterns were observed for the individual teratogenic drugs. The four drugs that increased the most were triptorelin (from 0.25% to 0.60%), follitropin α (from 0.35% to 0.59%), progesterone (from 0.82% to 1.07%) and paroxetine (from 0.85% to 1.01%).

Table 2: Dispensing rates per 1000 pregnancies for the potentially teratogenic drugs most frequently received during pregnancy

Potentially teratogenic drug	ATC code	In the 12-month period before conception (95% CI)	During pregnancy (95% CI)	During pregnancy in sensitivity analysis* (95% CI)
Any potentially teratogenic drug	N/A	156.87 (155.30 – 158.46)	50.71 (49.76 – 51.67)	61.35 (60.31 – 62.40)
Doxycycline	J01AA02	54.51 (53.53 – 55.50)	10.08 (9.65 – 10.52)	10.99 (10.53 – 11.44)
Paroxetine	N06AB05	17.25 (16.69 – 17.82)	8.54 (8.15 – 8.95)	10.07 (9.64 – 10.50)
Progesterone	G03DA04	16.16 (15.62 – 16.71)	8.23 (7.85 – 8.63)	10.67 (10.23 – 11.12)
Fluconazole	J02AC01	25.87 (25.19 – 26.57)	6.35 (6.02 – 6.71)	7.15 (6.78 – 7.51)
Follitropin α	G03GA05	9.71 (9.29 – 10.14)	3.54 (3.28 – 3.80)	5.85 (5.52 – 6.19)
Triptorelin (GrNH agonist, category X drug)	L02AE04	13.57 (13.07 – 14.08)	2.49 (2.28 – 2.71)	6.04 (5.70 – 6.37)
Norethisterone (category X drug)	G03DC02	15.53 (15.00 – 16.08)	2.17 (1.97 – 2.38)	2.53 (2.31 – 2.75)
Medrogestron - IM	G03DA02	12.33 (11.86 – 12.82)	1.55 (1.39 – 1.73)	2.04 (1.84 – 2.24)
Carbamazepine	N03AF01	1.56 (1.40 – 1.74)	1.24 (1.09 – 1.40)	1.29 (1.14 – 1.45)
Valproic acid	N03AG01	1.58 (1.41 – 1.76)	1.11 (0.98 – 1.26)	1.24 (1.08 – 1.39)
Dydrogesteron	G03DB01	4.35 (4.08 – 4.65)	1.03 (0.90 – 1.18)	1.23 (1.07 – 1.38)
Minocycline	J01AA08	3.72 (3.46 – 3.99)	1.03 (0.90 – 1.18)	1.30 (1.14 – 1.46)
Leuprorelin (GrNH agonist)	L02AE02	4.12 (3.85 – 4.41)	0.96 (0.83 – 1.10)	1.70 (1.52 – 1.87)
Acenocoumarol	B01AA07	1.26 (1.11 – 1.42)	0.89 (0.77 – 1.02)	1.08 (0.94 – 1.22)
Lynestrenol	G03DC03	4.95 (4.65 – 5.26)	0.86 (0.74 – 0.99)	1.05 (0.91 – 1.19)
Azathioprine	L04AX01	0.97 (0.84 – 1.11)	0.75 (0.63 – 0.87)	0.83 (0.70 – 0.95)
Tretinoin	D10AD01	1.87 (1.69 – 2.07)	0.56 (0.47 – 0.67)	0.67 (0.56 – 0.79)
Lamotrigine	N03AX09	0.57 (0.48 – 0.68)	0.55 (0.45 – 0.66)	0.60 (0.50 – 0.71)
Lithium	N05AN01	0.61 (0.51 – 0.73)	0.54 (0.45 – 0.65)	0.57 (0.47 – 0.67)
Hydrokinine	M09AA01	1.17 (1.03 – 1.33)	0.53 (0.44 – 0.64)	0.62 (0.51 – 0.73)

GrNH=gonadotropin-releasing hormone. CI=confidence interval.
**Including drugs dispensed before conception with a duration of use extending beyond conception date*

Figure 3: Pregnancies per 1000 pregnancies that received the most frequently received potentially teratogenic drugs per study period

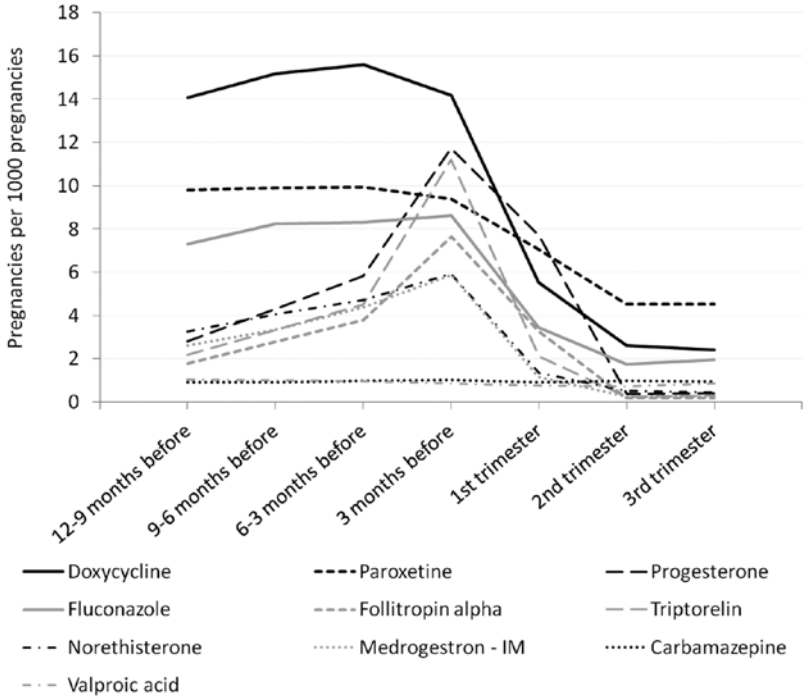


Table 3: Dispensing rates per 1000 pregnancies for the category X drugs most frequently received during pregnancy

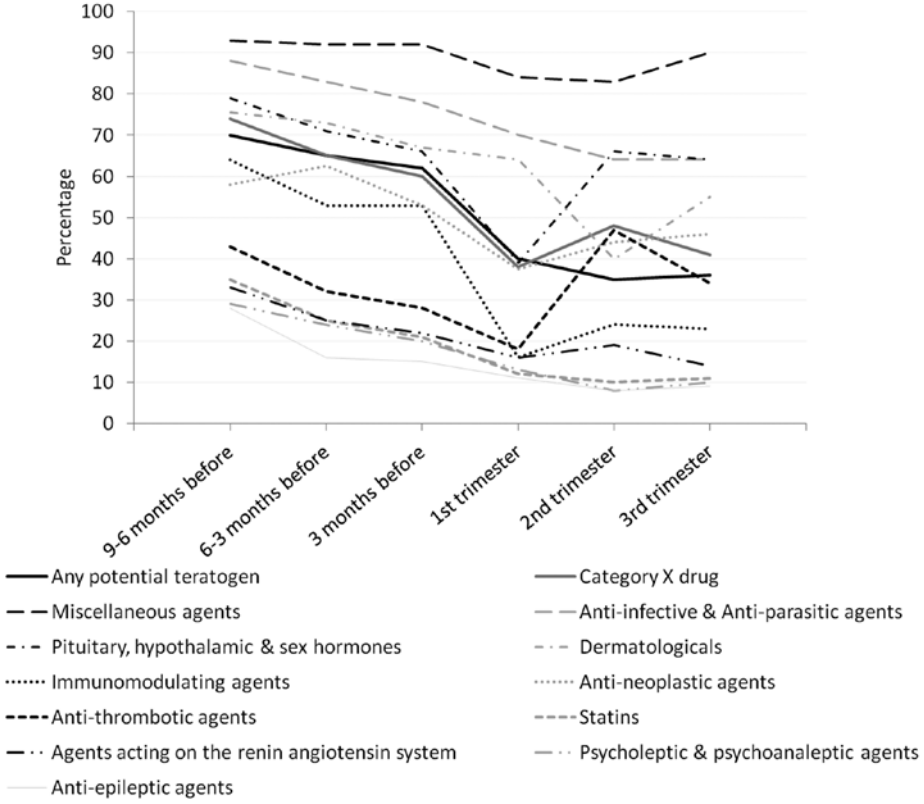
Category X drug	ATC code	In the 12-month period before conception (95% CI)	During pregnancy (95% CI)	During pregnancy in sensitivity analysis* (95% CI)
Any category X drug	N/A	35.10 (34.31 – 35.90)	6.62 (6.27 – 6.98)	11.87 (11.40 – 12.34)
Triptorelin (GrNH agonist)	L02AE04	13.57 (13.07 – 14.08)	2.49 (2.28 – 2.71)	6.04 (5.70 – 6.37)
Norethisterone	G03DC02	15.53 (15.00 – 16.08)	2.17 (1.97 – 2.38)	2.53 (2.31 – 2.75)
Simvastatin	C10AA01	0.78 (0.70 – 0.91)	0.31 (0.24 – 0.40)	0.46 (0.37 – 0.55)
Atorvastatin	C10AA05	0.91 (0.78 – 1.05)	0.25 (0.19 – 0.33)	0.48 (0.39 – 0.58)
Cetrorelix	H01CC02	0.60 (0.50 – 0.71)	0.25 (0.19 – 0.33)	0.35 (0.27 – 0.43)
Misoprostol	A02BB01	1.77 (1.59 – 1.95)	0.24 (0.18 – 0.32)	0.34 (0.26 – 0.42)
Nafarelin	H01CA02	1.29 (1.15 – 1.46)	0.21 (0.15 – 0.28)	0.63 (0.52 – 0.74)
Isotretinoin	D10BA01	0.50 (0.41 – 0.60)	0.20 (0.14 – 0.26)	0.23 (0.16 – 0.29)

GrNH=gonadotropin-releasing hormone. CI=confidence interval.
**Drug dispensed before conception which covered a period of use that overlapped pregnancy were considered*

Newly initiated drugs

In the periods before conception 60-70% of the pregnant women who received a potentially teratogenic drug received this for the first time during the study period (see Figure 4). These proportions decreased to 40.63% (15 of the 37 per 1000 pregnancies) in the first trimester of pregnancy, 35.87% (6 of the 16 per 1000 pregnancies) and 36.43% (6 of the 17 per 1000 pregnancies) in respectively the second and third trimester. Comparable proportions were observed for newly initiated category X drugs. Of the 5,463 pregnancies that received a newly initiated potentially teratogenic drug during pregnancy, which corresponds to 52.82% of all pregnancies that received a drug under study during pregnancy, the majority received doxycycline (3,039 pregnancies, 1.49% of all pregnancies) or fluconazol (1,678 pregnancies, 0.82% of all pregnancies). Of the 1,350 pregnancies that received a category X drug during pregnancy, 48% (649 pregnancies, 0.31% of all pregnancies) received this for the first time. The majority of the category X drugs newly initiated during pregnancy concerned triptorelin (131 pregnancies) and norethisterone (367 pregnancies). As presented in Figure 4, stratification per drug class showed heterogeneous proportions per drug class. The majority of the dispensed potentially teratogenic drugs classified as 'miscellaneous agents' (>80%) and 'anti-infective and anti-parasitic agents' (90 – 60%) were newly initiated. 'Psycholeptic and psychoanaleptic agents', 'anti-epileptic agents', 'statins' or 'agents acting on the renin angiotensin system' were less frequently newly initiated with 30 – 35% before pregnancy and 10% during pregnancy.

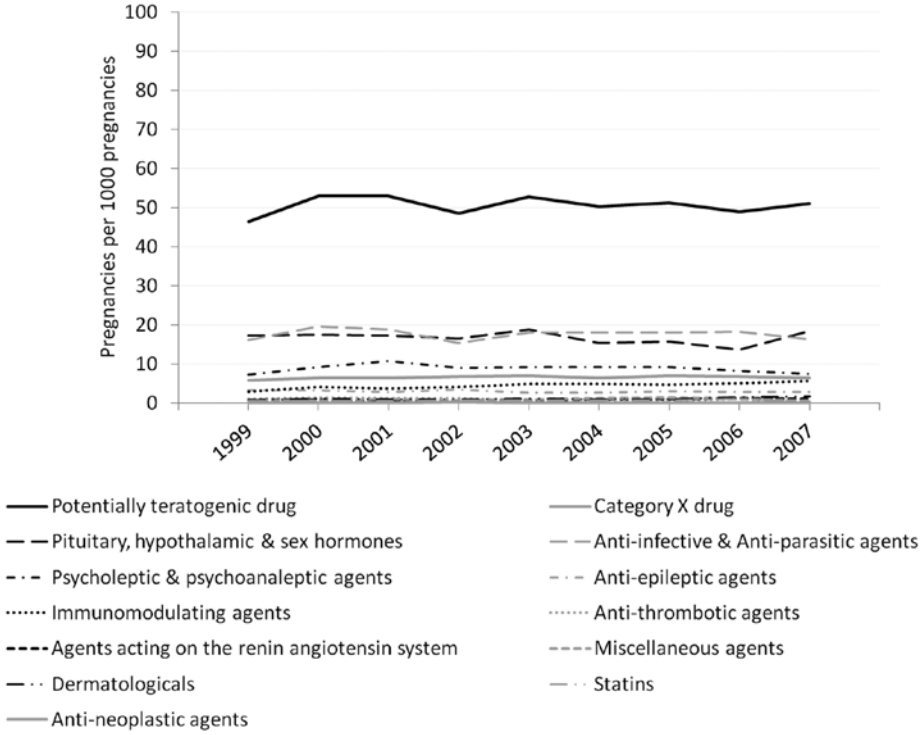
Figure 4: Among the exposed pregnancies, the percentage that received newly initiated drugs per exposure period and drug class



Change over time

Figure 5 illustrates the number of women that received potentially teratogenic drugs during pregnancy (first, second and third trimester) per year in the period 1999 – 2007. No changes in dispensing trend of potentially teratogenic drugs were observed over time with regard to the dispensing of any potentially teratogenic drugs, category X drugs and neither per drug classes.

Figure 5: Pregnancies per 1000 pregnancies that received potentially teratogenic drugs during pregnancy per calendar year and drug classes



DISCUSSION

Main findings

Between 1999 and 2007 in the Netherlands 77% of the pregnant women received a prescription drug in the 12-month period before pregnancy and 67% during pregnancy. Potentially teratogenic drugs were received by 16% of the pregnant women in the 12 months before conception and 5% of all women received these drugs during pregnancy. A small proportion, 0.7%, of the women received a category X drug during pregnancy. For 53% of the women who received potentially teratogenic drugs during pregnancy this considered newly initiated drugs. The decrease in the number of women who received potentially teratogenic drugs during pregnancy as compared to the period before conception was observed for the majority of potentially teratogenic drugs, which may be due to awareness of prescribers and patients of the potential fetal risks and the contraindications for use during pregnancy. However, still 5% of all pregnant women received a drug with teratogenic potential, the majority

during the first trimester, which is the most sensitive period for the developing fetus including the period of organogenesis.[21] In this early stage, women might not be aware of the pregnancy, resulting in fetal exposure to potentially teratogenic drugs.

Strengths and limitations

A strength of our study is the availability of detailed drug dispensing data from a year before conception until the end of pregnancy for a large cohort of more than 200,000 pregnancies which can be generalised to the Dutch population. Furthermore, the conception date could be obtained from the PRN database based on the last menstrual period or ultrasound, start and end dates of the 3-month study periods could be determined very accurately, and consequently the drug dispensing in those periods as well as the sensitivity analysis. A limitation of our study is that potentially teratogenic drugs used in hospital such as certain anti-neoplastic and immunodulating agents, are not captured in the community pharmacy dispensing data nor are over-the-counter medications. However, prescribed drugs by specialists in the outpatient setting are captured. Information on pregnancies that ended before a gestational age of 16 weeks, including spontaneous abortions and elective terminations of pregnancy, was not included in our study as the PRN database only contains information of pregnancies ≥ 16 weeks of gestation. This might have led to an underestimation of drug dispensing among the target population. The used classification systems to identify drugs with a teratogenic potential have shortcomings, e.g. the alphabetical order may incorrectly suggests a progression in risks from A to X, and categories do not always distinguish between differences in frequency, severity and type of fetal risk.[20] The evidence of teratogenic effect of some drugs remains uncertain, which suggests some misclassification of the potentially teratogenic drugs in our study, for instance for triptorelin and the anticoagulants. According to Van Gelder et al.,[22] 75 of the 202 potentially teratogenic drugs included in our study and 16 of the 39 category X drugs are known to have teratogenic mechanism. The uncertainty about teratogenic effects may also impact on the frequency of prescribing of the drugs under study. Nevertheless, although the classification systems have been criticised, they are useful for drug utilisation research in pregnancy.[23]

Interpretation

The 5.1% of the pregnant women who received a potentially teratogenic drug in our study is comparable to the findings of studies in other populations which ranged between 4.2 and 7.8%.[7-11, 24] Other Dutch studies also found that a considerable proportion of pregnant women received potentially teratogenic drugs.[12, 25] The study of Van Gelder et al.[25] among 32,016 Dutch pregnancies during the period from 1998 to 2009 showed that 18%, 21% and 33% of the pregnant women received drugs with potential teratogenic mechanisms in respectively the first, second or third trimester of pregnancy. Iron preparations, class III anti-arrhythmic drugs and tetracyclines contributed substantially to these high percentages, which were not all included in our study. These higher proportions compared to our study (overall 5.1%) can be explained by the different drugs that were examined.

Among the pregnancies that received a potentially teratogenic drug, the decreasing trend in percentages of pregnancies that received newly initiated drugs from before conception till the third trimester was expected considering the time factor in this analysis and the closed cohort. We observed variation in these proportions per therapeutic drug class which for some classes could be expected considering the indications of the drugs. Anti-infectives, the most frequently dispensed potentially teratogenic drugs in our study, are often for occasional, short term use what could explain the high proportions of pregnancies with newly initiated anti-infectives and in particular doxycycline. On the contrary, the anti-epileptics, statins, psycholeptic & psychonanaleptic agents and agents acting on

the renin angiotensin system have more chronic indications, which potentially lead to less treatment initiation during pregnancy (as observed for paroxetine, which was frequently dispensed but not often newly initiated), which is reassuring. For some drug classes as well as individual drugs the high proportions of newly initiated dispensings can be misleading as these correspond to a very low absolute number of pregnant women who received those drugs, i.e. for miscellaneous agents, dermatologicals and category X drugs (see Figure 2). Furthermore, the category X drugs newly initiated during pregnancy were mainly triptorelin and norethisterone, which are drugs used in fertility treatment and pregnancies in women receiving these drugs can therefore be expected, but initiating these therapies after conception seems inappropriate.

In the sensitivity analysis the proportion of pregnancy in which the mother received a potentially teratogenic drug increased from 5.1% to 6.1% when including pregnancies with a dispensing before conception with a duration of use extending beyond conception date. We observed that this increase which was mainly driven by frequently dispensed drugs used in assisted reproductive technology such as IVF: triptorelin, follitropin α and progesterone. These drugs, as expected by their indication, were most frequently received in the 3-month period before conception which explains, together with the overall high frequency of dispensing, the impact within the sensitivity analysis. As it can be expected that women only use these drugs until the IVF procedure and potential conception, our sensitivity analysis mainly adds untaken drugs to the analysis, resulting in an overestimation of the actual drug use.

Overall, potentially teratogenic drugs classified as reproductive hormones or GrNH agonists (triptorelin and leuprorelin) contributed substantially to the pregnancies during which a potentially teratogenic drug was received (30%). As expected by their indication, these drugs were mainly received before pregnancy. The obvious peak in the number of women that received potentially teratogenic drugs in the 3-month period before conception was most probably the result of the GrNH agonists and other fertility agents used in IVF including progesterone and follitropin α. When triptorelin and leuprorelin were received during pregnancy, this was mainly (in 85% and 86%, respectively) during the first trimester of pregnancy as expected, when the women might not be aware of the pregnancy. Antibiotics are often used during pregnancy and in our study 'anti-infectives and anti-parasitic agents' were also the most commonly received potentially teratogenic drugs before and during pregnancy.[26] Doxycycline, an antibiotic that is contraindicated during pregnancy because of the known effects on bone and tooth development in the fetus, was most frequently received during pregnancy (in 10 per 1000 pregnancies).[27] Paroxetine, a selective serotonin reuptake inhibiting antidepressant, is the second most frequently dispensed potentially teratogenic drug during pregnancy in our study. In 2005, the European regulatory authorities highlighted the possible association between maternal paroxetine exposure in the first trimester of pregnancy and cardiovascular malformations in the developing fetus via a direct healthcare professional communication.[28] Although some studies observed increased risks on congenital heart defects after paroxetine use in early pregnancy, the absolute risk for the hearth defects remains small.[29-31] The risks on congenital malformations have been studied for other selective serotonin reuptake inhibitors, with often inconclusive results.[32-36] Discontinuation of antidepressants in pregnant women may not always be appropriate and the consequences of untreated major depression might impact the mother and the unborn child and the treatment of depression may outweigh the potential fetal harm. Therefore, the most appropriate therapy should be determined at individual patient level considering the potential beneficial and harmful effects of the treatment. In general, as with other chronic medical conditions such as epilepsy or diabetes mellitus, drugs with teratogenic potential should only be used during pregnancy after a balanced decision.

The category X drugs received during pregnancy mainly concerned triptorelin, a fertility agent,

and norethisterone, a drug with several indications: dysfunctional uterine bleeding, endometriosis, polymenorrhoea, menorrhagia, metropathia, haemorrhagia, postponement of menstruation and premenstrual syndrome. These drugs may be classified in category X due to their lack of benefit of use during pregnancy. Furthermore, triptorelin can also be used for preoperative reduction of myoma size to reduce the symptoms of bleeding and pain in women with symptomatic uterine myomas. This patient population should not be or become pregnant when an uterine surgery is planned which may also explain the category X of this drug, rather than a potential teratogenic effect, especially since evidence of harmful effects of triptorelin on the fetus is not available. Next to these, statins were the most frequently received category X drugs during pregnancy (0.07% of the pregnancies). Statins are labelled category X due to potential effects on the development of the fetus as observed in animal studies, plus the hypothesis that treatment of dyslipidemia offers no benefit for pregnant women. However, studies in animals and human show conflicting evidence on the teratogenic effects of statins.[37] The potential risks of statin use during pregnancy require further investigation.

Of particular concern is the dispensing of the highly teratogenic drug isotretinoin to 40 pregnant women (0.20 per 1000 pregnancies). The majority (33 of the 40) received the drug even more than once during pregnancy while the isotretinoin pregnancy prevention programme aims to have no isotretinoin-exposed pregnancies. Although the number of observed exposed pregnancies is relatively low, it adds to the evidence that isotretinoin-exposed pregnancies occur despite the strict measures to prevent this. Isotretinoin-exposed pregnancies were also observed in a French and Canadian study.[38, 39] In addition, previous studies identified challenges for implementation of the pregnancy prevention programme in the EU and US.[40-42] In the Netherlands, concomitant use of contraceptives and isotretinoin is, although higher than the background use (48%), still relatively low among women of reproductive age (59%).[43] All these findings suggest that the current pregnancy prevention programme may not be completely effective.

Conclusions

A considerable proportion of Dutch pregnancies (5%) received a potentially teratogenic drug during pregnancy and 0.7% a category X drug, of which in 53% of these pregnancies was newly initiated therapy. Drugs with teratogenic potential should be used during pregnancy only after a balanced decision in which potential benefits and harms are carefully weighed. It may be possible to reduce these proportions in future, especially since in the Netherlands only 42% of the women of reproductive age using potentially teratogenic drugs used concomitant contraceptive measures, which could lead to unnecessary teratogenic drug exposure during pregnancy.[4] Future research is necessary to explore reasons for teratogenic drug prescription and dispensing to pregnant women in order to develop targeted measures to minimise unnecessary drug exposure if appropriate.

Appendix I: Overview of the definitions of the pregnancy classifications of the ADEC, FASS and FDA

Category	The former Australian Drug Evaluation Committee (ADEC)	The Swedish Catalogue of Approved Drugs (FASS)	Pregnancy Classification ot the Food and Drug Authority (FDA)
A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.	Medicinal products which may be assumed to have been used by a large number of pregnant women and women of child-bearing age without any identified disturbance in the reproductive process, e.g. an increased incidence of malformations or other direct or indirect harmful effect on the fetus.	Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. B1 Studies in animals have not shown evidence of an increased occurrence of fetal damage. B2 Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage. B3 Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.	Medicinal products which may be assumed to have been used by only a limited number of pregnant women and women of child-bearing age, without any identified disturbance in the reproductive process having been noted so far, e.g. an increased incidence of malformations or other direct or indirect harmful effect on the fetus. B1 reproduction toxicity studies have not given evidence of an increased incidence of fetal damage or other deleterious effects on the reproductive process B2 reproduction toxicity studies are inadequate or lacking, but available data do not indicate an increased incidence of fetal damage or other deleterious effects on the reproductive process B3 reproduction toxicity studies in animals have revealed an increased incidence of fetal damage or other deleterious effects on the reproductive process, the significance of which is considered uncertain in man.	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal reproduction studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on	Medicinal products which by their pharmacological effects have caused, or must be suspected of causing,	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled

	the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.	disturbances in the reproductive process that may involve risk to the fetus without being directly teratogenic. If experimental studies in animals have indicated an increased occurrence of fetal injuries or other injurious effects on the reproductive process of uncertain significance in humans, these findings are to be stated in this category.	studies in humans, but potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risk.
D	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.	Medicinal products which have caused an increased incidence of fetal malformations or other permanent damage in man or which, on the basis of e.g. reproduction toxicity studies, must be suspected of doing so. This category comprises drugs with primary teratogenic effects. If the product also has pharmacological effects that may directly or indirectly have a harmful effect on the fetus, this must also be stated.	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.	Not applicable	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks of the use of the drug in pregnant women clearly outweighs any possible benefit.

Appendix II: Classification of 202 potentially teratogenic drugs into eleven different therapeutic area

Group	Name	ATC-code	ADEC	FASS	FDA
Anti-infective & Anti-parasitic agents	Albendazole	P02CA03	D	n.a.	C
	Amikacin	J01GB06	D	D	D
	Artemether	P01BE52	D	n.a.	C
	Artemether	P01BE02	D	n.a.	C
	Chloroquine	P01BA01	D	B3	n.a.
	Cidofovir	J05AB12	D	D	C
	Demeclocycline	J01AA01	D	n.a.	D
	Doxycycline	A01AB22	D	n.a.	D
	Doxycycline	J01AA02	D	D	D
	Efavirenz	J05AG03	D	D	D
	Fluconazole	J02AC01	D	B3	C
	Ganciclovir	J05AB06	D	D	C

Group	Name	ATC-code	ADEC	FASS	FDA
Anti-infective & Anti-parasitic agents	Albendazole	P02CA03	D	n.a.	C
	Amikacin	J01GB06	D	D	D
	Artemether	P01BE52	D	n.a.	C
	Artemether	P01BE02	D	n.a.	C
	Chloroquine	P01BA01	D	B3	n.a.
	Cidofovir	J05AB12	D	D	C
	Demeclocycline	J01AA01	D	n.a.	D
	Doxycycline	A01AB22	D	n.a.	D
	Doxycycline	J01AA02	D	D	D
	Efavirenz	J05AG03	D	D	D
	Fluconazole	J02AC01	D	B3	C
	Ganciclovir	J05AB06	D	D	C
	Gentamicine	J01GB03	D	D	D
	Hydroxychloroquine	P01BA02	D	B3	n.a.
	Minocycline	J01AA08	D	n.a.	D
	Neomycin	A07AA01	D	n.a.	n.a.
	Neomycin	J01GB05	D	n.a.	D
	Netilmicin	J01GB07	D	D	D
	Oxytetracycline	J01AA06	D	D	n.a.
	Primaquine	P01BA03	D	n.a.	n.a.
	Quinine	P01BC01	D	D	C
	Ribavirin	J05AB04	D	D	X
	Streptomycine	J01GA01	n.a.	n.a.	D
	Tetracycline	A01AB13	D	n.a.	D
	Tetracycline	J01AA07	D	D	D
	Tigecycline	J01AA12	D	D	D
	Tobramycin	J01GB01	D	B3	D
	Valganciclovir	J05AB14	D	D	C
	Zalcitabine	J05AF03	D	n.a.	C
Agents acting on the renin angiotensin system	Benazepril	C09AA07	n.a.	n.a.	D
	Candesartan	C09CA06	D	D	D
	Captopril	C09AA01	D	D	D
	Cilazapril	C09AA08	D	n.a.	n.a.
	Enalapril	C09AA02	D	D	D
	Eprosartan	C09CA02	D	D	D
	Exforge	C09DB01	D	D	D
	Fosinopril	C09AA09	D	n.a.	C
	Irbesartan	C09CA04	D	D	C
	Lisinopril	C09AA03	D	D	D
	Losartan	C09CA01	D	D	C
	Olmesartan	C09CA08	D	n.a.	C
	Perindopril	C09AA04	D	D	D
	Quinapril	C09AA06	D	D	D
	Ramipril	C09AA05	D	D	D
	Telmisartan	C09CA07	D	D	C
	Trandolapril	C09AA10	D	n.a.	C
	Valsartan	C09CA03	D	D	D
Anti-thrombotic agents	Acenocoumarol	B01AA07	n.a.	n.a.	n.a.
	Fenprocoumon	B01AA04	n.a.	n.a.	n.a.
	Warfarin	B01AA03	D	D	X
Statins	Atorvastatin	C10AA05	D	D	X
	Fluvastatin	C10AA04	D	B3	X

	Pravastatin	C10AA03	D	B3	X
	Rosuvastatin	C10AA07	D	D	X
	Simvastatin	C10AA01	D	B3	X
Dermatologicals	Aciretin	D05BB02	X	D	X
	Adapalene	D10AD03	D	B3	C
	Finasteride	D11AX10	X	D	X
	Isotretinoin	D10BA01	X	n.a.	X
	Tazaroteen	D05AX05	D	n.a.	X
	Tetracycline	D06AA04	D	n.a.	B
	Tretinoin	D10AD01	D	B3	C
Pituitary, hypothalamic & sex hormones	Carboprost	G02AD04	D	n.a.	C
	Cetrorelix*	H01CC02	D	C	X
	Danazol*	G03XA01	D	n.a.	X
	Dutasteride	G04CB02	D	n.a.	X
	Dydrogesteron*	G03DB01	D	n.a.	n.a.
	Estrogens, esterified*	G03CA57	D	n.a.	X
	Finasteride	G04CB01	D	D	X
	Follitropin alpha*	G03GA05	D	B1	n.a.
	Ganirelix*	H01CC01	D	C	X
	Gestrinon*	G03XA02	D	n.a.	n.a.
	Levonorgestrel	G02AC03	B3	n.a.	X
	Lynestrenol*	G03DC03	D	D	n.a.
	Medrogestron – IM*	G03DA02	D	D	n.a.
	Medroxyprogesterone and estrogen*	G03FA12	D	B3	X
	Medroxyprogesterone and estrogen*	G03FB06	D	B3	X
	Mesterolon*	G03BB01	D	n.a.	n.a.
	Nafarelin*	H01CA02	D	B3	X
	Nomegestrol*	G03DB04	D	n.a.	n.a.
	Norethisterone*	G03DC02	D	D	X
	Progesterone*	G03DA04	D	n.a.	n.a.
	Raloxifene*	G03XC01	D	D	X
	Testosterone*	G03BA03	D	D	X
	Tetracosactide	H01AA02	D	C	n.a.
	Tibolon*	G03CX01	D	B3	n.a.
Anti-neoplastic agents	Alitretinoin	L01XX22	n.a.	n.a.	D
	Altretamine	L01XX03	D	n.a.	D
	Amsacrine	L01XX01	D	D	n.a.
	Bevacizumab	L01XC07	D	D	C
	Bleomycin	L01DC01	D	D	n.a.
	Bortezomib	L01XX32	C	D	D
	Busulfan	L01AB01	D	D	D
	Capecitabine	L01BC06	D	D	D
	Carboplatin	L01XA02	D	D	D
	Carmustine	L01AD01	D	n.a.	D
	Cetuximab	L01XC06	D	B2	C
	Chlorambucil	L01AA02	D	D	D
	Cisplatin	L01XA01	D	D	D
	Cladribine	L01BB04	D	D	D
	Clofarabine	L01BB06	n.a.	D	D
	Cyclophosphamide	L01AA01	D	D	D
	Cytarabine	L01BC01	D	D	D

Group	Name	ATC-code	ADEC	FASS	FDA
	Dacarbazine	L01AX04	D	D	C
	Dactinomycin	L01DA01	D	n.a.	C
	Dasatinib	L01XE06	D	B3	D
	Daunorubicin	L01DB02	D	D	D
	Docetaxel	L01CD02	D	D	D
	Doxorubicin	L01DB01	D	D	D
	Epirubicin	L01DB03	D	D	D
	Erlotinib	L01XE03	C	B3	D
	Estramustine	L01XX11	D	n.a.	n.a.
	Etoposide	L01CB01	D	D	D
	Fludarabine	L01BB05	D	D	D
	Fluorouracil	L01BC02	D	D	D
	Gemcitabine	L01BC05	D	D	D
	Hydroxycarbamide	L01XX05	n.a.	D	n.a.
	Idarubicin	L01DB06	D	D	D
	Ifosfamide	L01AA06	D	D	D
	Imatinib	L01XE01	D	B3	D
	Irinotecan	L01XX19	D	B3	D
	Lapatinib	L01XE07	n.a.	B3	D
	Lomustine	L01AD02	D	D	D
	Melphalan	L01AA03	D	D	D
	Mercaptopurine	L01BB02	D	D	D
	Methotrexate	L01BA01	D	D	X
	Mitomycine	L01DC03	D	D	D
	Mitoxantrone	L01DB07	D	D	D
	Nelaribine	L01BB07	n.a.	D	D
	Oxaliplatin	L01XA03	D	D	D
	Paclitaxel	L01CD01	D	D	D
	Pemetrexed	L01BA04	D	D	D
	Pentostatin	L01XX08	n.a.	n.a.	D
	Procarbazine	L01XB01	D	n.a.	D
	Raltitrexed	L01BA03	D	n.a.	n.a.
	Sorafenib	L01XE05	D	C	D
	Streptozocine	L01AD04	n.a.	n.a.	D
	Sunitinib	L01XE04	D	B3	D
	Tegafur	L01BC03	D	n.a.	n.a.
	Temozolomide	L01AX03	D	D	D
	Teniposide	L01CB02	D	n.a.	D
	Thioguanine	L01BB03	D	D	D
	Thiotepa	L01AC01	D	n.a.	D
	Topotecan	L01XX17	D	D	D
	Tretinoin	L01XX14	X	n.a.	D
	Vinblastine	L01CA01	D	D	D
	Vincristine	L01CA02	D	D	D
	Vindesine	L01CA03	D	D	n.a.
	Vinorelbine	L01CA04	D	D	D
Immunomodulating agents	Aminoglutethimide	L02BG01	D	n.a.	D
	Azathioprine	L04AX01	D	D	D
	Basiliximab	L04AC02	D	B2	B
	Daclizumab	L04AC01	D	n.a.	C
	Fulvestrant	L02BA03	D	D	D
	Goserelin	L02AE03	D	D	D

	Interferon Beta 1a	L03AB07	D	D	C
	Interferon Beta 1b	L03AB08	D	D	C
	Leflunomide	L04AA13	D	D	X
	Lenalilomide	L04AX04	n.a.	D	X
	Letrozole	L02BG04	D	B3	D
	Leuprorelin*	L02AE02	D	C	n.a.
	Medrogestron IM	L02AB02	D	D	n.a.
	Megestrol	L02AB01	D	B3	X
	Mycophenolic acid	L04AA06	D	D	D
	Penicillamine	M01CC01	D	n.a.	D
	Tamoxifen	L02BA01	B3	D	D
	Tasonermine	L03AX11	D	B2	n.a.
	Thalidomide	L04AX02	D	D	X
	Toremifene	L02BA02	B3	B3	D
	Triptorelin*	L02AE04	D	B3	X
Anti-epileptic agents	Carbamazepine	N03AF01	D	D	C
	Ethosuximide	N03AD01	D	D	n.a.
	Lamotrigine	N03AX09	D	B3	C
	Methylfenobarbital	N03AA01	D	n.a.	n.a.
	Oxcarbazepine	N03AF02	D	D	C
	Phenobarbital	N03AA02	D	D	D
	Phenytoin	N03AB02	D	D	n.a.
	Primidone	N03AA03	D	n.a.	n.a.
	Sultiam	N03AX03	D	n.a.	n.a.
	Valproic acid	N03AG01	D	D	D
	Vigabatrin	N03AG04	D	D	C
Psycholeptic & psychoanaleptic agents	Amobarbital	N05CA02	n.a.	n.a.	D
	Butabarbital	N05CA03	n.a.	n.a.	D
	Lithium	N05AN01	D	n.a.	n.a.
	Paroxetine	N06AB05	D	C	D
	Pentobarbital	N05CA01	n.a.	n.a.	D
	Secobarbital	N05CA06	n.a.	n.a.	D
Miscellaneous agents	Acetohydroxac acid	G04BX03	n.a.	n.a.	X
	Ambrisentan	C02KX02	X	D	X
	Bosentan	C02KX01	D	D	X
	Deferipron	V03AC02	D	n.a.	n.a.
	Dihydroergotamine	N02CA01	C	C	X
	Ergotamine	N02CA02	C	n.a.	X
	Hydrokinine	M09AA01	D	n.a.	n.a.
	Ivrabradine	C01EB17	D	D	n.a.
	Misoprostol	A02BB01	X	D	X
	Nandrolone	A14AB01	D	n.a.	X
	Nicotine	N07BA01	D	C	C
	Oxandrolone	A14AA08	D	n.a.	X
	Prasteron	A14AA07	D	n.a.	n.a.
	Retinol	A11CA01	D	n.a.	n.a.
	Tretinoin	A01AD11	D	n.a.	D

**These reproductive hormones, ovulation stimulants or fertility drugs were excluded from some analyses*
n.a.=not applicable

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9

SUMMARY AND GENERAL DISCUSSION

GENERAL DISCUSSION

During the last decade the risk management approach towards drugs has evolved and it is still a very dynamic area. Major developments started with the introduction of the risk management plan (RMP) in 2005. The RMP of a drug describes the planned pharmacovigilance activities and risk minimisation measures that have been agreed between the marketing authorisation holder (MAH) and regulatory authorities. Risk minimisation measures (RMMs) are interventions that aim to optimise the benefit-risk balance of a drug by minimising its risks during drug use in daily practice. These measures intend to prevent or reduce the occurrence or the severity of adverse drug reactions (ADRs).[1] *Routine* RMMs are required for all drugs and include the Summary of Product Characteristics (SmPC), the patient information leaflet (PIL), the labelling (packaging), the pack size and the legal (prescription) status of a drug. While for the majority of drugs routine RMMs adequately addresses the safety concerns of the drug, sometimes extra measures beyond those routinely required are necessary to minimise the drug related risks during use in clinical practice, i.e., the *additional* risk minimisation measures (aRMMs). Examples of aRMMs are educational tools for healthcare professionals (HCPs) or patients and a pregnancy prevention programme (PPP).

For each new active substance licensed in the European Union (EU) after 2005 a RMP has been agreed and the need and the possibilities for aRMMs have been evaluated on a case-by-case basis. From that time, industry and regulators have gained experience in the field of risk minimisation measures and also with additional risk minimisation measures. With the EU pharmacovigilance legislation in place since July 2012 new standards in the EU risk management approach were set and monitoring the effectiveness of the risk minimisation measures in real world practice became mandatory.[2, 3] However, the knowledge on how to measure the effectiveness of aRMMs in routine care is still quite limited.

This thesis provides further insight into the quality and quantity of the additional risk minimisation measures required in the EU and how the effectiveness of these measures in clinical practice can be evaluated. In this chapter the results of the studies presented in this thesis are summarised and discussed, followed by a description of the lessons learned so far and future perspectives in the area of evaluation of effectiveness of aRMMs in clinical practice.

MAIN FINDINGS

Additional risk minimisation measures in the EU

Chapter 2 provides an overview of the aRMMs required in the EU at 1 January 2010. This analysis showed that aRMMs were required for 58 of the 391 (15%) active substances authorised in the EU between 1 January 1995 and 1 January 2010 through the centralised procedure. The proportion of the active substances with aRMMs increased from 5% to 29% of the active substances approved in the period before compared to the period after the RMP was introduced. In the five years after the introduction of RMPs, aRMMs were most frequently required for antineoplastic and immunomodulating agents. The main requested additional risk minimisation strategy was provision of educational materials, which was required for all drugs with aRMMs, always addressed to HCPs and for approximately 50% of the drugs with aRMMs educational material was also requested for patients. Other measures such as a controlled distribution system or a PPP were less frequently required, for 17% and 9% of the active substances included in the analysis, respectively. An important finding of this review was the limited consistency in required aRMMs across similar safety concerns. Exceptions were teratogenicity and hepatotoxicity, where in all instances a PPP and patient monitoring was required. The increase in aRMMs may point to an increasing awareness of MAHs and regulators to the available options of minimising risks. The

growing number of drugs with aRMMs as well as the hope that these indeed will lead to less safety issues or adverse reactions, emphasizes the need for evaluation of the effectiveness of these measures.

Using electronic healthcare databases for the evaluation of effectiveness of aRMMs

aRMMs are aimed to minimise potential harms related to drugs and may also add an extra burden on the healthcare system. Ineffective measures should be modified in early stages and not unnecessary burden clinical practice. This shows the clear need for rapid evaluation and timely feedback on the intended and unintended effects of aRMMs in clinical practice to allow modification of the aRMMs in an early stage. Since existing electronic healthcare record databases (EHDs) present opportunities to rapidly investigate drug-event associations as well was drug utilisation patterns, we explored whether these resources can be used to evaluate the effectiveness of aRMMs in clinical practice (**Chapter 3**). Existing electronic healthcare record databases refer to already existing computerised data sources containing routinely collected medical information from actual care and which are commonly used for pharmacoepidemiology and pharmacovigilance research.[4, 5] There is wide variation between EHDs and these can include administrative (claims) databases, routine primary care databases, but also specific disease and drug registries. Data included in EHDs varies per EHD but the information considered generally retrievable from existing EHDs include: patient demographics, information regarding drug prescription/dispensing, medical events which can include adverse events, symptoms/signs, diagnosis in primary care, specialist diagnosis, hospital discharge diagnosis, laboratory values, death, clinical procedures, overdoses and teratogenic events.[4, 5] The key elements of the aRMMs of the 68 drugs with aRMMs authorised in the EU via the centralised procedure between 1 January 1995 and 1 April 2011 were reviewed. These key elements are the core components of the aRMMs to be implemented in all EU member states. Of the 801 aRMM key elements reviewed (median number of key elements per drug was 9.5), 36% aimed provision of knowledge and 57% recommended an action (a behavioural change) of HCPs or patients. Considering the information generally retrievable from existing EHDs, only a limited proportion (22%) of the aRMM key elements are considered suitable for evaluation in existing EHDs. These key elements mainly aimed at behavioural changes of HCPs. It particularly concerned recommendations to perform regular laboratory tests or patient examinations or recommendations regarding drug prescription, e.g. dose recommendations, contraindications. The key elements that we considered not measurable in EHDs were either poorly drafted and unclear measures (11%) or the data necessary for evaluation was not considered available in existing EHDs. The latter included aRMM key elements that aimed to provide knowledge to HCPs or patients regarding the benefit-risk profile of a drug (34%), to introduce behavioural changes in patients (15%) or recommended actions that HCPs should take regarding drug administration (11%). The majority of aRMM key element was not considered suitable for assessment in existing EHDs and it remains a challenge to evaluate the effectiveness of these aRMMs in an efficient and objective way using data sources other than EHDs. Well-defined aRMM key elements with clear objectives leading to unambiguous actions of the target group should be agreed by industry and regulatory authorities. Improvement of the quality of the aRMMs could facilitate the assessment of effectiveness of aRMMs in routine care.

The evaluation of implementation and effectiveness of aRMMs in clinical practice can comprise different levels, which are described in **Chapter 4**. These levels involve 1) the assessment of risk minimisation tool dissemination and use, 2) measuring the knowledge of HCPs or patients as well as 3) evaluation of the desired behaviour of HCPs or patients (e.g., prescription behaviour or compliance to patient monitoring). These levels evaluate the implementation and use of the aRMMs in clinical practice and are considered the process indicators of the aRMMs. In addition to the process indicators, 4) the actual risk reduction of a safety outcome to be minimised can be assessed, which is the so-called outcome indicator of the aRMM. This chapter also described specific challenges in measuring the effectiveness

of risk minimisation measures. These include appropriate data collection via EHDs or surveys, lack of comparators when aRMMs are implemented since initial marketing authorisation, uncertainty on the best outcome measures and its interpretation, and the lack of benchmarking or pre-defined aRMM objectives. Considering these challenges, the best feasible methodology for evaluating the effectiveness of aRMMs can differ per drug or type of aRMM.

Recommended dose restrictions of citalopram

The impact of risk minimisation measures on the use of citalopram in United Kingdom (UK) and the Netherlands (NL) is evaluated in **Chapter 5**. Citalopram is an antidepressant and available in the EU since the early nineties. In October 2011 European regulatory authorities recommended citalopram dose restrictions based on new information on a dose dependent QT interval prolongation that was associated with this drug.[6] The maximum daily dose of citalopram was reduced from 60 mg to 40 mg and in elderly patients (aged ≥ 65) from 40 mg to 20 mg. This was communicated to HCPs with a Direct Healthcare Professional Communication (DHPC) while the product information of citalopram was updated.[7-9] The following primary care databases were used: THIN (The Health Improvement Network from UK) and IPCI database (Interdisciplinary Processing of Clinical Information from NL), covering a period ranging from 1996 to 2013. We analysed the use of the following three daily dose categories for citalopram in the general population: low (≤ 20 mg); moderate (>20 to ≤ 40 mg); high (> 40 mg). New users of citalopram and those that continued using citalopram after the new dose recommendations were analysed separately. Over the entire study period the monthly prevalence rate of citalopram use was higher in UK compared with NL and independent of country and age group, monthly prevalence rates were highest for citalopram low dose and very low for high dose citalopram. With an interrupted time-series analysis using an ARIMA (autoregressive integrated moving average) model we observed that after the dose restrictions, the use of citalopram with moderate dosages significantly decreased among the elderly in UK and NL which in British elderly was also observed for high dose citalopram. Among the British and Dutch population younger than 65 years only the use of high dose citalopram significantly reduced. Independent of country and age categories, a large majority of patients using citalopram at 31 October 2011 continued using the same daily dose, including high dosages. In both countries a decrease in elderly people starting citalopram after the dose restrictions was observed. This latter finding is considered an additional, unintended effect of the risk minimisation measures.

Risk minimisation measures and drug exposure during pregnancy

The safe use of drugs in pregnant women is of specific interest in view of the potential serious risks on spontaneous abortion and birth defects after drug exposure in this vulnerable population. Pregnant women are generally excluded from most clinical trials and knowledge about the safety of drugs during pregnancy is usually not established at the moment of first marketing. Proactive pharmacovigilance and risk management during the post-marketing period is therefore important to not only characterise, but also to minimise the possible risks for the developing embryo or fetus. aRMM that can be imposed to minimise the risk of drug exposure during pregnancy and its serious consequences is the pregnancy prevention programme (PPP). In **Chapter 6** we explored the reasons to request PPPs in the EU and the elements used in these PPPs. At time of the study seven drugs in the EU had a PPP, that have been developed per drug on a case-by-case basis: thalidomide and lenalidomide; the vitamin A derivatives isotretinoin, acitretin and alitretinoin; bosentan and ambrisentan (endothelin receptor antagonists). The PPPs of thalidomide, lenalidomide and the vitamin A derivatives have been imposed based on an established or expected high teratogenic risk in humans. For bosentan and ambrisentan, the rationale for the imposed PPP was less clearly documented. Not all drugs with known human teratogenic risks

have a PPP or an absolute contraindication for use such as the antiepileptic drugs valproic acid or carbamazepine.[10, 11] For these therapies the potential treatment benefits may outweigh the potential risks because discontinuation of these therapies may be harmful for both the mother and the unborn child. Similarities as well as differences among risk minimisation measures taken for teratogenic drugs exist. The seven PPPs contained similar elements including pregnancy tests before and monthly during drug use; contraceptive use and pregnancy prevention counselling of patients. The differences between PPPs concerned educational materials for different target groups, restricted drug supply, continuation of contraceptive use and pregnancy tests after treatment discontinuation. The latter can be explained by the half-life time of the drug. In addition to such drug-specific characteristics, previous experiences as well as the feasibility in clinical practice should be considered in the development of a programme. The latter can be done by involving prescribers, pharmacists and patients. It may also be helpful to provide regulatory guidance on standard (minimum) requirements that should always be part of the PPP and optional elements (depending on the target population and drug specific characteristics) of PPPs in the European guideline on human reproduction and lactation.[12]

Isotretinoin pregnancy prevention programme

Effectiveness of the isotretinoin PPP has previously been studied and in these studies the compliance with the isotretinoin PPP was less than optimal.[13, 14] In **Chapter 7** we examined the occurrence of isotretinoin exposure in Dutch pregnant women despite the mandatory PPP and we analysed the occurrence of adverse fetal or neonatal outcomes (intrauterine deaths ≥ 16 weeks of gestation or live borns with major congenital malformations). A cohort of 203,962 pregnancies between 1999 and 2007 consisting of 208,161 fetuses was constructed using a linkage between the PHARMO Database Network and the Netherlands Perinatal Registry (PRN). There were 45 of these pregnancies, 2.2 (95%CI 1.6 to 2.9) per 10,000 pregnancies, exposed to isotretinoin during pregnancy. Sixty percent of isotretinoin exposed pregnancies women started isotretinoin while already pregnant. Adverse fetal or neonatal outcomes potentially related to isotretinoin were identified for 9.4% (95% CI 1.3 to 17.6) of the isotretinoin exposed pregnancies. The OR for adverse fetal or neonatal outcomes after isotretinoin exposure in 30 days before or during pregnancy was 2.3 (95% CI 0.9 to 5.7) which should be carefully interpreted because low numbers were involved and no adjustments for important confounding factors other than maternal age could be made. Furthermore, spontaneous abortions that occurred in the period until 16 weeks of gestation were not included in our study. It was concluded that although a PPP was already implemented in 1988, isotretinoin exposed pregnancies and adverse fetal and neonatal events potentially related to the exposure still occur. These findings from the Netherlands add to the evidence that there is no full compliance to the isotretinoin PPP in many Western countries. Given the limited success of iPLEDGE, the even stricter isotretinoin PPP implemented in the United States (US), the question is which measures are able to further improve compliance.

Dispensing of drugs with teratogenic potential to pregnant women

In **Chapter 8** we examined the dispensing of potentially teratogenic drugs in the 12 month period before as well as during pregnancy in the same cohort of Dutch pregnancies as described in Chapter 7. 202 drugs with either a Swedish Catalogue of Approved Drugs (FASS) 'D' classification, the former Australian Drug Evaluation Committee (ADEC) or US Food and Drug Administration (FDA) 'D' or 'X' classification were considered potentially teratogenic. Category X drugs should not be used during pregnancy since the risks clearly outweigh the potential benefits. Sixteen percent of the 203,962 pregnancies received a potentially teratogenic drug in the 12 month period before and 5.1% during pregnancy. Doxycycline and paroxetine were most frequently received during pregnancy by 1.01% and 0.85% of women, respectively; 0.66% of the women received a risk category X drug

during pregnancy which most frequently consisted of triptorelin (0.25%), norethisterone (0.22%), and simvastatin (0.03%). Fifty-tree percent of the women who received a potentially teratogenic drug during pregnancy received this for the first time during the study period. The majority of the dispensed potentially teratogenic drugs classified as 'anti-infective and anti-parasitic agents' were newly initiated whilst 'Psycholeptic and psychoanaleptic agents', 'anti-epileptic agents', 'statins' or 'agents acting on the renin angiotensin system' were less frequently newly initiated: 30 – 35% were initiated before pregnancy and approximately 10% during pregnancy. Heterogeneity between these percentages can be explained by the shorter and occasional use of anti-infectives compared to chronic use of antidepressants and anti-epileptics. It can be concluded that a considerable proportion of 5% of the pregnancies received a potentially teratogenic drug during pregnancy and 0.7% a drug from the risk category X. Drugs with teratogenic potential should be used during pregnancy only after a balanced decision in which potential benefits and harms are carefully weighed. It may be possible to reduce these proportions in future, especially since in the Netherlands only 42% of the women of reproductive age using potentially teratogenic drugs used concomitant contraceptive measures, which could lead to unnecessary teratogenic drug exposure during pregnancy.[15] Future research is necessary to explore reasons for teratogenic drug prescription and dispensing to pregnant women in order to develop targeted measures to minimise unnecessary drug exposure if appropriate.

KNOWLEDGE ON EFFECTIVE aRMMs IS STILL LACKING

The growing experience with aRMMs over the years provided insight in the possibilities and challenges of aRMMs in clinical practice as well as evaluating the effectiveness of aRMMs. In addition to the practical experience obtained by regulators, industry and academics, several initiatives contributed knowledge to this field. With the EU pharmacovigilance legislation in place since July 2012 new standards in the EU risk management approach were set and Good Vigilance Practice Module XVI was developed to provide guidance on evaluation of risk minimisation measures.[1] In addition, the report 'Practical approaches to risk minimisation for medicinal products' of the Council for International Organisations of Medical Sciences (CIOMS) Working Group IX has recently been published.[16] Furthermore, the work in this thesis and other scientific publications provide useful information on how effectiveness of aRMMs can be evaluated and the challenges involved.

However, knowledge on effective aRMMs is still limited because only a few studies evaluating aRMMs or the US risk evaluation and mitigation strategies (REMS) of a specific drug have become available in the scientific literature. Since evaluation of the effectiveness of aRMMs became a legal obligation in the EU in 2012, evaluations of recent aRMMs may be still be in progress and therefore not yet available in the public domain. The studies that have been published often concern the implementation and effectiveness of the PPP or direct healthcare professional communications (DHPCs).[13, 14, 17-29] Other studies evaluated the REMS for varenicline, the REMS for long-acting $ß_2$-adrenergic agonist (LABA) and the recommended screening for latent tuberculosis (TB) prior to initiation of tumour necrosis factor-alpha (TNF-α) antagonists.[30-33] More examples concern routine risk minimisation measures such as the evaluation of the effect of the paracetamol pack size reduction in UK to a maximum of 32 tablets in pharmacies and to 16 tablets for non-pharmacy sales on the deaths due to paracetamol overdose.[34] An Italian study evaluated the effectiveness of recommendations (new maximum daily dose and recommended echocardiograph before start and every 6 months) that were added to the SmPC for cabergoline to reduce the risk of cardiac valvulopathy in clinical practice.[35]

A few systematic reviews addressed the methodologies that have been used to study the impact of regulatory interventions.[36-39] Piening et al. and Dusetzina et al. reviewed studies evaluating the impact of drug safety warnings including black box warnings or dear doctor letters in the US and DHPC in

the EU.[36, 39] Another review included also studies that evaluated risk minimisation interventions other than safety warnings such as the PPP or patient monitoring or examination.[37] The review of Briesacher et al. included evaluations of FDA safety warnings, label changes and drug withdrawals that used methodologies applicable in administrative claim databases only, so studies using surveys or other primary data collection were excluded.[38] Because studies on effectiveness of aRMMs or REMS are still very limited, the systematic reviews mainly included evaluations of risk communications such as DHPCs and FDA safety communications and particularly with regard to antidepressants, rosiglitazone and cisapride. Nevertheless, knowledge on possible methodologies to assess the impact of drug safety warnings is relevant to consider in the evaluation of effectiveness of aRMMs as discussed in the next section.

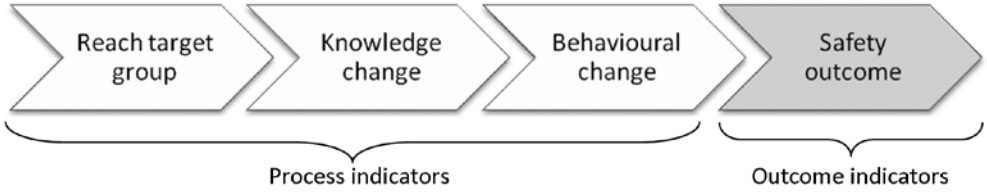
EVALUATION OF EFFECTIVENESS OF aRMMs IN CLINICAL PRACTICE: THE ESSENTIALS

The evaluation of the effectiveness of aRMMs in clinical practice basically starts with understanding the objective of the aRMMs. Once it is clear what the aRMM aims to achieve, the following main components necessary to evaluate effectiveness of aRMM should be carefully considered by regulators, industry and academics: the outcome measures, data sources and analytical methods to use in the evaluation. These essentials for evaluating the effectiveness of risk minimisation measures are discussed below using experiences from the studies presented in this thesis as well as in published literature.

What to achieve: objectives of the aRMMs

Understanding the objective of the aRMM is necessary to determine an outcome that could truly measure the effectiveness of the aRMM. Recommendations leading to unambiguous actions of the target group (e.g. HCPs or patient) that would prevent or reduce the risk of the event in clinical practice can more easily be translated into objectives and expectations of the aRMMs, which facilitate the implementation and effectiveness evaluation of aRMMs in clinical practice. Therefore, specific and clearly drafted aRMM key elements which, if possible, lead to actions should be agreed by industry and regulatory authorities. Sometimes several objectives could be suggested for the aRMM. For example for the isotretinoin PPP these include: 1) knowledge on the teratogenic risk of isotretinoin and on the strategies to prevent pregnancy; 2) compliance with prescription and use of contraceptives during isotretinoin treatment in young women; and the final objective: 3) no isotretinoin exposed pregnancies. Guidance on these different aspects of the risk minimisation process (Figure 1) and the evaluation of effectiveness are provided in the European Good Vigilance Practice Module XVI.[1] This process starts with the fact that an aRMM should reach the target group: for instance the distribution of educational material to HCPs or patients. Once read, used and understood, the target group should be knowledgeable on serious risks of the drug and how to use it appropriately. Next, the target groups should implement the desired behaviour if that is recommended. All together, these aspects should result in a lower risk on the occurrence of a harmful event (e.g., isotretinoin exposed pregnancy) which is considered the final objective of the aRMMs.

Figure 1: the process of risk minimisation in four levels



What outcome to evaluate

The main question is which objective and corresponding outcome should be studied to evaluate effectiveness of aRMMs in clinical practice. Prieto et al.[40] described a model that documents the effectiveness of risk minimisation measures evaluating process as well as outcome indicators. This dual evidence approach has been incorporated in the European guidance on risk minimisation measures and is generally in line with the risk minimisation process as indicated in Figure 1. The process indicators evaluate the implementation of RMMs which include evaluation of level of knowledge of HCPs and patients and compliance to clinical actions or behaviour of HCPs or patients. With the outcome indicators the effect on the occurrence or severity of the ADRs to be minimised in clinical practice can be determined. Another model presents five different steps to measure effectiveness of aRMMs and each level results in another outcome with increasing utility of information, i.e. (1) risk minimisation tool coverage, (2) risk minimisation tool awareness and use, (3) risk knowledge and comprehension, (4) behavioural modification, (5) safety outcomes.[41]

The systematic reviews of studies evaluating the effects of DHPCs, FDA risk communications and some other risk minimisation interventions showed that the majority of evaluations assessed behavioural modifications such as prescription behaviour and mainly overall drug use or drug use in specific patient populations.[36, 37, 39] The impact of the intervention on knowledge and the occurrence of adverse events (safety outcome) was assessed infrequently. A minority of the studies included in these reviews evaluated multiple process indicators or outcome indicators.[37, 39] Drug exposure data (prescription behaviour) is frequently used as process indicator of behavioural change but may result in crude estimates of the effectiveness of risk minimisation measures which becomes more informative when more specific drug use outcomes are used by stratification for e.g. special patient populations, new users, indication, duration of use or prescribed dose. To reflected the prescription behaviour of HCPs of citalopram, we studied several process outcomes (Chapter 5): prevalent and incident use of citalopram in the general population, the distribution of the daily dose categories among all citalopram users as well as effect on use in continuing citalopram users after the recommended dose restrictions. However, there may still be additional relevant outcomes related to citalopram prescription that could have been studied. When studying process indicators it is not simply knowledge or behaviour that can be evaluated. Within these areas there are many possible outcomes that can be used to study effectiveness of aRMMs of which the most appropriate should be used. Specific and clear pre-defined objectives leading to actions should facilitate the determination of the most suitable process indicators. The use of appropriate outcome indicators (safety outcome) of interest should be considered (e.g. a surrogate endpoint such as an adequate biomarker as a substitute for a clinical endpoint) if such an approach facilitates the effectiveness evaluation.[1] While the safety outcome of the isotretinoin PPP, isotretinoin exposed pregnancies, is an acute event and quite clear, the most appropriate outcome to study can be more open for discussion when it concerns a biomarker (e.g. liver function levels) or an event that can have different stages of severity (e.g. impaired vision towards blindness). The challenge is to measure the occurrence of an event that should not occur anymore. Pharmacoepidemiological approaches should be applied to study different type of safety outcomes including acute events or events that gradually develop over time. Pharmacoepidemiological studies may be less informative when there is still considerable uncertainty with regard to the drug-event association. When the safety outcome to be studied is very rare, it may be challenging to indicate a risk reduction as we would aim to demonstrate almost a zero risk.

Appropriate data sources

Effectiveness of aRMMs can be studied using different type of data sources. As an example, the awareness of TB risk, performance of TB screening and factors predicting TB screening among prescribers of TNF-α antagonists (infliximab, adalimumab, etanercept, golimumab, certolizumab) in multiple EU member states were studied using data from prescriber surveys.[33, 42] In contrast, the data from a Spanish registry of patients with rheumatic diseases treated with TNF-α antagonists allowed assessment of automatically, longitudinal data, but in only one country.[30] The type of data used for the evaluation of aRMMs and the possible impact on the validity of the results, time planning, possible outcome measures or other potential biases should be well considered by researchers, regulators and MAHs. Existing electronic healthcare databases (EHDs) present good opportunities to rapidly investigate drug-event associations and are commonly used for pharmacoepidemiology and pharmacovigilance research.[43, 44] EHDs contain longitudinal routinely collected data reflecting actual care of a broad patient population. Using this data is efficient and timely feedback on the aRMM may be provided which allows adjustment of aRMMs in early stages. It is known that EHDs are frequently used to evaluate the effectiveness of risk communications and particularly to study drug prescribing (behavioural outcomes) and sometimes also safety outcomes.[36, 37, 39] It is preferred to study these outcome measures using data obtained from existing EHDs because of the efficiency and validity of using data from EHDs as well as the higher utility of information from behavioural outcomes and safety outcomes compared to information on reaching the target group or knowledge. However, as observed in Chapter 3, only 22% of the key elements of aRMMs may potentially be measurable in EHDs because these data sources do not capture all data necessary data for the evaluation. Furthermore, some EHDs may not be appropriate since the number of subjects using the particular drug with aRMMs available in EHDs can be limited or grow slowly. This is particularly of concern for drugs that recently entered the market or are used for treating serious disease in hospital and therefore not recorded in primary care databases, which is likely for drug with aRMMs. These issues indicate that there is a clear need for approaches that go beyond the use of EHDs to allow evaluation of effectiveness of aRMMs. These can include surveys or qualitative assessments which are often used to evaluate whether aRMMs reached the target group and the achieved level of knowledge among this target group.[36, 37] The use of surveys is the main method of data collection among the studies evaluating effectiveness of risk minimisation measures that are included in the EU PAS Registry.[45] Some limitations of this approach are that data collection can be time consuming and delay the evaluation whereas insufficient aRMMs need to be identified in an early stage to enable prompt improvement. Furthermore, response rates to surveys are often low and the responses may not reflect the actual knowledge, awareness or use of aRMMs among the target group which may prevent drawing valid conclusions from the assessment of aRMM's effectiveness.[46, 47]

Other possible data sources that may be used to evaluate the effectiveness of aRMMs in clinical practice are the spontaneous reporting systems as these include case reports of patients that developed adverse events. These systems lack however a suitable overall denominator (i.e., total exposure to the drug, number of patients exposed or number of drug doses administered), which inevitably hampers interpretation of results. Furthermore, it is known that reporting of ADRs can be influenced in different ways by external events.[48] It may be that aRMMs increase the intention to report events to these systems. The use of spontaneous reports in the evaluation of aRMM may therefore not be suitable.

Analytical methods

To analyse impact of regulatory interventions issued post-marketing, data from the pre-intervention period can be compared against the post-intervention period, a time series analysis or other regression

analysis can be performed e.g. linear regression, Poisson regression, joint point regression.[36] A requirement of such analysis is the use of longitudinal data on prescription or patient level which often are obtained from existing EHDs to study drug prescription patterns or safety outcomes. Briesacher et al. identified three analytic methods with strong internal validity suitable for evaluations of regulatory actions which include the interrupted time series, the regression discontinuity design, and the statistical method, the extended Cox model.[38] While the interrupted time series analysis is frequently applied to evaluate the impact of DHPCs, FDA risk communications and some other regulatory interventions,[36, 38, 39] experiences with the last two approaches have not yet been available in the literature and experience is needed to assess the actual feasibility of these methods. All three approaches described by Briesacher et al. have the ability to control for other factors and can incorporate intention-to-treat analyses.[38] Interrupted time series design is preferred to study the impact of policy changes where it is difficult to employ a comparison group, and account for potential biases in the effect of the intervention including secular trend, seasonal effects, random fluctuations and autocorrelations.[49] However, for aRMMs required since initial marketing authorisation an interrupted time series analysis or a pre-post intervention analysis cannot be applied and effectiveness may be evaluated by comparing the observed against expected outcomes. Expected outcomes can be pre-defined reference values or benchmarks obtained from literature, historical data, frequencies in general population, other geographical location or centres where the intervention was not implemented, another drug or other target population (e.g. adults when the intervention is aimed at children).[37] A study on use of cisapride with contraindicated drugs is an example where reference values were obtained from the study population.[50] The observed co-prescribing of cisapride with potentially interacting drugs was compared to the chance of having a co-prescription based on background prevalence of cisapride and potentially interacting drugs (the expected). When it may not be feasible to involve comparators or assess changes after a certain point in time, the evaluation of aRMMs could be restricted to descriptive analysis using a cohort covering a period of time or a cross-sectional analysis. Such descriptive analysis are used in the isotretinoin study in Chapter 7 of this thesis in which the annual incidence of isotretinoin exposed pregnancies in the Netherlands between 1999 – 2007 was studied without having a comparison group. Changes after the implemented intervention could also not be analysed because the PPP was implemented during the complete study period. Information collected with surveys usually provides cross-sectional information on knowledge or behaviour at one point in time unless the survey is repeated over time among the same participants.

Selecting the most appropriate settings

In summary, several outcome measures, data sources and analytical methods can be used to study the effectiveness of risk minimisation measures which all have specific strengths and weaknesses and the most appropriate settings may depend on the type of drug, aRMM or event to be minimised. The challenge is developing and systematically utilizing robust methodologies for evaluation of aRMMs effectiveness. First, specific and clear pre-defined objectives of aRMMs are necessary to determine the most appropriate process and outcome indicators. Second, preference is given to behavioural indicators and safety outcomes that can be studied using existing EHDs. EHDs are considered valid and efficient resources that can provide timely feedback on the effectiveness of aRMMs. However, since EHDs do not capture all data necessary to study the different process and outcome indicators, approaches beyond the use of EHDs should be used and it is a challenge to do this in an efficient and proper way. The interrupted time series analysis and pre-post intervention analysis are frequently used statistical methods for evaluation of regulatory intervention implemented during post-marketing such as DHPCs. Since aRMMs are often required from initial marketing authorisation these analytical methods cannot always be applied and the possibilities of other comparators in the evaluation of aRMMs need to be explored.

FUTURE PERSPECTIVES

The past 10 years after starting RMPs have led to a better understanding of the possibilities and challenges of aRMM implementation and the evaluation of effectiveness in clinical practice. Very clearly this field is still developing since there is still limited knowledge on effective aRMMs in clinical practice; what can be achieved with aRMMs and the best way of achieving this. Furthermore, besides measuring the effectiveness (benefits) of aRMMs in clinical practice, the actual burden and the additional load of aRMMs, should be explored. This burden may impact access to medicines, daily activities of patients or HCPs and human and financial resources.

There is a need for transparency about effective aRMMs and validated tools as well as on evaluations of effectiveness of aRMMs. Besides sharing results of studies in scientific literature, study protocols and final study reports can be obtained from the publicly available EU PAS register hosted by ENCePP.[45] This E-registry includes all non-interventional PASS relating to medicines which will become more populated and can be used as learning opportunities.

Role for the regulator

Without having standard requirements available, regulators should carefully review the need for aRMMs. This is a case-by-case assessment and the extra measures should be adequately justified, proportionate to the risk and feasible in clinical practice. Previously, (based on the Guideline on risk management systems of 2005), the MAH had to justify why aRMMs were not necessary, suggesting that aRMMs were needed by default.[51] This approach changed with the EU pharmacovigilance legislation in force since July 2012 and since that time it should be justified why routine risk minimisation measures are not considered sufficient and why aRMMs are necessary.[52] This approach as well as the increased knowledge on aRMMs in general may have resulted in different proposals for aRMMs as compared to the situation up to 2010. The legal obligation to measure the effectiveness of aRMMs might have contributed to this.

In one of our studies we observed that the objectives of aRMMs were not always clear. This requires attention of regulators because specific and clear objectives of the aRMMs are an essential starting point in the design of the required PASS that evaluate the effectiveness of aRMM. Next, regulators should carefully consider what knowledge is needed to decide on the successfulness of the measures and critically review how and when this can be obtained in a feasible, efficient and valid way leading to useful results. Finally, regulators should engage with HCPs and patients from clinical practice to explore what would be effective aRMMs, how to define success and to decide on when and how to continue or modify aRMMs in clinical practice.

Effective aRMMs

For the drugs we evaluated in Chapter 3, educational materials were the main strategy which can comprise many different educational tools such as a brochure, checklist, website or a patient alert card. However, knowledge on the effectiveness of aRMMs in clinical practice, or more specifically, educational tools in addition to the SmPC, is still lacking. More research is necessary to evaluate the effectiveness of specific risk minimisation tools. Furthermore, the development of the most appropriate aRMM tools and strategies requires involvement of stakeholders from clinical practice and insights in local conditions. Industry and regulators should engage with patients and HCPs (e.g. physicians, pharmacists, etc) and explore if, when and how (not) HCPs and patients let aRMMs be integrated in clinical practice. Knowledge from other disciplines such as behavioural and communication science

could also contribute to this. It would also be relevant to identify factors associated with sustained responses to communication and to investigate how aRMMs can affect communication between HCPs and patient. There might be substantial variation in preferences of the need for, the format and distribution of the materials between different prescribers, pharmacists and patients populations.

How to define success

Knowledge about the effectiveness of aRMMs is necessary to determine the success of the additional measures and to decide on the need for continuation and potential adjustments of the aRMMs. As discussed in the previous sections of this chapter, there are various possibilities to evaluate the effectiveness of aRMMs in which different process and outcome indicators, data sources and analytical methods can considered which all have their strengths and limitations. Because methodological challenges exist, it may still be open for discussion what type of study is necessary to define the successfulness of aRMMs. Other issues are:

Acceptable levels for successful aRMM are often not defined and it is not always clear when an aRMMs could be labelled as successful. An option is to consider aRMM successful only when the risk of a particular safety outcome is completely eliminated meaning that the event (e.g. isotretinoin exposed pregnancy) does not occur in the patient population treated. It may however not be realistic to use such a 'zero tolerance' strategy to estimate aRMM successfulness. Even with full compliance to the aRMMs the event may develop in patients using that drug independently and moreover, noncompliance with the aRMM could be a carefully made decision of the HCP and patient. It should also be noted that significant changes in knowledge, behaviour or safety outcomes after aRMM implementation or differences between patient populations do not automatically indicate a successful aRMM. It still needs to be assessed whether the level of compliance to aRMMs or occurrence of the safety outcome is acceptable. For example, as observed in Chapter 5, the significant reduction of moderate dose citalopram use (>20 mg – ≤ 40 mg) daily among patients aged 65 or older may not be large enough because still a considerable proportion of the elderly patient population is using these daily doses (since longer time) when the change in SPC arrives. With regard to the assessment of acceptable levels of clinical knowledge among HCPs, it may be better to achieve that 75% of the prescribers respond correct to 8 out of 10 survey questions instead of reviewing the percentage of prescribers that have all survey questions correct. Regulators and industry should explore acceptable and feasible levels for success by involving HCPs and patients working with aRMMs in clinical practice. The most optimal and acceptable levels of compliance to aRMMs (i.e. process indicators) and of its final outcome measures (occurrence of events) in clinical practice may vary across different drugs.

It has become more and more clear that regulatory actions cannot only have intended effects, but may also have unintended consequences. The need for laboratory monitoring may result in decreased drug use and recommendations that are targeted at specific patient population may also diffuse in other groups.[36] Following the warning of the increased risk of suicide associated with antidepressant use in children and adolescents in 2004, a decrease in use of this antidepressant was also observed in adults.[53-56] Furthermore, long-term effects of this warning suggested that the risk communication was followed by a decrease in antidepressant use but with an increase in suicides.[56] The warning may has unintentionally discouraged depressed patients from seeking treatment, which may even be more harmful.[57] For these reasons understanding the possible unintended effects of risk communication and risk minimisation measures is important and should be considered in decisions to be made.

What and when to evaluate

The most appropriate process and outcome indicators or combinations to define successfulness of aRMMs should facilitate justified decisions on the continuation or modification of the aRMMs. However, the most appropriate outcomes to estimate effectiveness may not always be the most feasible outcome to study. Providing early feedback on the occurrence of rare events or events that develop after long-term drug exposure can be challenging since drug use shortly after drug marketing is limited. When feedback on the final safety outcome is not feasible, it may be easier to provide (preliminary) results of the process indicators only or provide results on the safety outcome in a later stage. There is need to explore the most appropriate point in time after aRMM implementation that provides early feedback as well as adequate data for evaluation. This can be done based on previous experiences in evaluation of effectiveness, driven by minimum patient exposure or based on providing sample size calculations necessary to indicate certain effects. It may be helpful to develop standard time schedules and frequencies to provide follow-up on the effectiveness of aRMMs to prevent evaluations leading to insufficient results.

Causality and extrapolation

In addition to the difficulties with data collection of appropriate outcome measures and definitions of successful aRMMs, other issues that could complicate the interpretation of the study results concern the uncertainty in the causality between the process indicators, final safety outcomes and the implemented aRMM. This uncertainty is difficult to overcome with the current way of aRMM implementation and the study designs available to study effectiveness of interventions in routine daily care. Sometimes aRMMs have been implemented for a complete drug class or several generic compounds (e.g. the new oral anticoagulants). For these drugs it may be difficult to assess whether it is the aRMM of the single drug under review that is contributing to the study results or it may be the combination of aRMMs of drugs from the same class.

The need for aRMM is often decided on European level while the implementation of the aRMM takes place locally to take into account national requirements, e.g. health systems, language and health believes. This national phase allows better-fitting programmes. In current regulatory practice the effectiveness of aRMMs is often measured in only some of the EU member states, due to e.g. available electronic healthcare databases and sales per EU member state. Variation in clinical practice and implementation of aRMMs between EU member states limit extrapolation of the results on effectiveness of risk minimisation measures to all EU member states. However, the heterogeneity between member states also provide opportunities to study differences in aRMM implementation and the effect of this.

Does this finally lead to aRMM (dis)continuation and modification

When to stop and how long to continue with aRMMs is an area that deserves attention and requires involvement of different stakeholders. The results of the evaluations of the effectiveness of aRMM could lead to various conclusions on continuation or modification of the aRMMs. When results show sufficient effectiveness, the aRMM may be continued, or even discontinued when the measure has become standard care. When the effectiveness of aRMMs is considered limited, the aRMM may not be continued or possibilities to improve the effectiveness may be identified. Reasons for failure and improvement of aRMMs can sometimes be identified using the process indicators measured within the evaluation or with root cause analysis by involving stakeholders from clinical practice.

CONCLUSION

Evaluating effectiveness of aRMM is recognised to be a relatively young but evolving area with no universally agreed standards and approaches. Knowledge and experience on how the effectiveness can be evaluated and the challenges involved have been gained. Specific and clear objectives of aRMMs are necessary and the most appropriate and feasible outcomes to estimate intended and unintended effects of aRMMs in clinical practice should be determined. Since knowledge on effective aRMMs is still very limited there is a need to continuously share experiences on effective risk minimisation and methodologies to evaluate the effectiveness of the measures. Furthermore, more research is necessary to better understand what can be achieved with aRMMs in clinical practice and when aRMMs can be considered successful. This is needed for an adequate assessment of the need for aRMMs and selection of the most appropriate tools as well as to facilitate the decision on the (dis)continuation or modification of aRMMs implemented in clinical practice. Industry, regulators and stakeholders from clinical practice should engage and advantage should be taken from relevant methods in drug utilisation research, pharmacoepidemiology and other disciplines such as behavioural and communication sciences.

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9

NEDERLANDSE SAMENVATTING

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Het College ter Beoordeling van Geneesmiddelen (CBG) beoordeelt en bewaakt de werkzaamheid, risico's en kwaliteit van geneesmiddelen voor mens en dier. Het CBG neemt een positie in binnen de Europese geneesmiddelen registratieautoriteiten. Wanneer op basis van een klinisch onderzoeksprogramma de werkzaamheid-schadelijkheid balans van een geneesmiddel positief is bevonden, kan er een handelsvergunning verstrekt worden en mag het geneesmiddel toetreden tot de markt. Het is echter van belang om, nadat een geneesmiddel op de markt beschikbaar is, de kennis over de werkzaamheid en schadelijkheid van een geneesmiddel verder uit te breiden met ervaringen uit de klinische praktijk. Daarom worden de werkzaamheid-schadelijkheid balans en vastgestelde voorwaarden voor geneesmiddelgebruik continue geëvalueerd en zo nodig aangepast. Farmacovigilantie speelt hierin een belangrijke rol. De Wereldgezondheidsorganisatie (WHO) definieert farmacovigilantie als de *wetenschap en activiteiten gerelateerd tot het opsporen, beoordelen, begrijpen en voorkomen van bijwerkingen of andere problemen die verbanden houden met gebruik van geneesmiddelen.*

De afgelopen 10 jaar heeft farmacovigilantie zich ontwikkeld tot een aandachtsgebied waarin het minimaliseren van risico's gerelateerd aan een geneesmiddel een prominentere rol heeft gekregen. De grote veranderingen startten met de introductie van het risico management plan (RMP) in 2005. Het RMP van een geneesmiddel beschrijft de geplande farmacovigilantie en risico minimalisatie maatregelen die zijn overeengekomen tussen de vergunninghouder van een geneesmiddel (farmaceutische industrie) en de Europese registratieautoriteiten.

Risico minimalisatie maatregelen (RMM) zijn interventies die de balans werkzaamheid-schadelijkheid van een geneesmiddel optimaliseren tijdens geneesmiddelgebruik in de dagelijkse praktijk. Deze maatregelen hebben als doel nadelige effecten (bijwerkingen, medicatie fouten) van een geneesmiddel te voorkomen, de kans op deze effecten te verkleinen, of de ernst van een nadelig effect te verlagen, mocht dit optreden. Routine RMM worden vastgesteld voor alle geneesmiddelen en omvatten de Samenvatting van Product Kenmerken (SmPC), de patiënten bijsluiter (PIL), het uiterlijk van de verpakking, de verpakkingsgrootte en de voorschrijfstatus van het geneesmiddel. Hoewel *routine* RMM voldoende zijn voor de meeste geneesmiddelen, kunnen extra maatregelen soms nodig zijn om de veiligheidsissues van een geneesmiddel te beperken. Deze worden *aanvullende* risico minimalisatie maatregelen (aRMM) genoemd en worden vastgesteld in de handelsvergunning als voorwaarde voor gebruik van een geneesmiddel in de praktijk. Voorbeelden van deze aanvullende maatregelen zijn voorlichtingsmaterialen voor artsen, apothekers of patiënten, of een zwangerschap-spreventie programma (ZPP).

Voor elk geneesmiddel met een nieuw actief bestanddeel dat een handelsvergunning in de Europese Unie (EU) heeft verkregen na 2005 is een RMP vastgesteld. Per geneesmiddel is er beoordeeld of aRMM nodig zijn en welke mogelijkheden voor aRMM er zijn. Vanaf 2005 doen de vergunninghouders en de registratieautoriteiten dus ervaring op in het veld van risico minimalisatie maatregelen en de aanvullende maatregelen. Met ingang van de Europese wetgeving in 2012 is het meten van de effectiviteit van de risico minimalisatie maatregelen in klinische praktijk verplicht. Echter, de kennis over hoe de effectiviteit van aRMM in dagelijkse praktijk gemeten kan worden is nog erg beperkt.

Dit proefschrift geeft inzicht in de kwaliteit en kwantiteit van de aanvullende risico minimalisatie maatregelen die van kracht zijn in de EU en hoe de effectiviteit van deze maatregelen in de dagelijkse praktijk geëvalueerd kan worden. Er wordt dieper in gegaan op de risico minimalisatie maatregelen van teratogene geneesmiddelen (in het bijzonder het ZPP) en blootstelling aan geneesmiddelen met teratogene eigenschappen tijdens de zwangerschap.

Aanvullende risico minimalisatie maatregelen (aRMM) in de EU

Hoofdstuk 2 geeft een overzicht van de aRMM vastgesteld in de EU tot 1 januari 2010. Van de geneesmiddelen geregistreerd voordat het RMP van kracht was had 5% aRMM en van de geneesmiddelen geregistreerd na de introductie van het RMP (2005) had 15% aRMM. Dit betroffen voornamelijk oncologische geneesmiddelen en geneesmiddelen die het afweersysteem beïnvloeden. Het meest gevraagde type aRMM was voorlichtingsmateriaal voor artsen, apothekers of andere zorgverleners. In 50% van de gevallen werd er ook voorlichtingsmateriaal voor de patiënt gevraagd. Een gecontroleerd distributie systeem of een ZPP was minder vaak gevraagd, respectievelijk voor 17% en 9% van de geneesmiddelen met aRMM. Er bleek weinig consistentie te zijn in de veiligheidsissues waar de aRMM voor zijn vastgesteld. Zowel het groeiend aantal geneesmiddelen met aRMM als de hoop dat deze maatregelen ook daadwerkelijk tot minder bijwerkingen of andere veiligheidsissues zouden leiden, benadrukt de noodzaak tot het evalueren van de effectiviteit van deze maatregelen.

Het gebruik van bestaande databanken van elektronische patiëntendossiers om de effectiviteit van aRMM te evalueren

aRMM hebben als doel de schadelijke effecten van een geneesmiddel te beperken, maar deze extra maatregelen kunnen de klinische praktijk ook belasten. Ineffectieve aRMM dienen daarom in een zo vroeg stadium geïdentificeerd en aangepast te worden. Dit geeft aan dat er behoefte is aan een efficiënte methode om de effectiviteit van de aRMM te beoordelen. Bestaande databanken van elektronische patiëntendossiers, zoals geanonimiseerde patiëntendossiers van de huisarts of apotheek uitgifte gegevens van receptgeneesmiddelen die routinematig worden verzameld, bieden mogelijkheden om relatief snel associaties tussen een geneesmiddel en een bijwerking te bestuderen. Ook kunnen op populatieniveau patronen in geneesmiddelgebruik in klinische praktijk bestudeerd worden. In **Hoofdstuk 3** is onderzocht of deze databanken ook geschikt kunnen zijn om de effectiviteit van aRMM te evalueren. Gezien de informatie beschikbaar in bestaande databanken van elektronische patiëntendossiers, schatten wij dat 22% van de hoofdelementen van de aRMM meetbaar zijn in deze gegevensbronnen. Voornamelijk elementen gerelateerd aan het voorschrijfgedrag van artsen (zoals dosering, duur, contra-indicatie) en intensiever monitoren van de patiënt (zoals bloedwaarde testen) zijn meetbaar bevonden. Het blijft een uitdaging om de effectiviteit van de andere aRMM op een efficiënte en objectieve manier te evalueren waarbij andere gegevens dan die beschikbaar in bestaande databanken van elektronische patiëntendossiers gebruikt moeten worden. Goed gedefinieerde aRMM hoofdelementen met heldere doelen die leiden tot eenduidige acties van de doelgroepen (zorgverleners of patiënten) zullen door vergunninghouders en registratieautoriteiten moeten worden gedefinieerd om de evaluatie van aRMM te faciliteren.

De verschillende stappen binnen een evaluatie van de effectiviteit van aRMM in de dagelijkse klinische praktijk zijn beschreven in **Hoofdstuk 4**. Deze stappen omvatten 1) beoordeling van de distributie en gebruik van de risico minimalisatie tool, 2) meten van de verkregen kennis onder zorgverleners of patiënten, 3) evalueren van het gewenste gedrag van zorgverleners of patiënten (bijvoorbeeld het voorschrijfgedrag van de arts of het intensief monitoren van de patiënt). Deze stappen evalueren de implementatie en gebruik van de aRMM in de dagelijkse praktijk en worden ook wel 'proces indicatoren' genoemd. Naast de proces indicatoren kan 4) de actuele risico verlaging van een veiligheidsissue gemeten worden, dat ook wel de 'uitkomst indicator' van de aRMM wordt genoemd (zie Figuur 1). Mogelijke uitdagingen in het meten van de effectiviteit van aRMM staan ook beschreven in dit hoofdstuk en omvatten geschikte dataverzameling, beperkte mogelijkheid tot vergelijken van groepen, onzekerheid over de beste uitkomstmaat en de interpretatie, en gebrek aan vooraf vastgestelde doelen. Gezien deze uitdagingen kan de best uitvoerbare methode om de effectiviteit

van aRMM te evalueren verschillen per geneesmiddel of soort aRMM.

In **Hoofdstuk 5** is de effectiviteit van de risico minimalisatie maatregelen van een specifiek geneesmiddel bestudeerd. In oktober 2011 werd bekend dat het gebruik van hoge doseringen citalopram (een antidepressiva) kan leiden tot verlenging van het QT interval, wat zich kan uiten in (fatale) hartritmestoornissen. De aanbevolen maximale dagelijkse dosering werd toen verlaagd van 60 mg naar 40 mg en in ouderen (≥ 65 jaar) van 40 mg naar 20 mg. Deze risico informatie is gecommuniceerd aan artsen via een brief, een zogenaamde DHPC (Direct Healthcare Professional Communication). Het gebruik van citalopram tussen 1996 en 2013 en het mogelijke effect van de DHPC en aanbevolen doseringsverlaging zijn geanalyseerd. Hiervoor is gebruik gemaakt van de Nederlandse Interdisciplinary Processing of Clinical Information (IPCI) databank en het Britse The Health Improvement Network (THIN); beide longitudinale databanken van elektronische patiëntendossiers van huisartsen. We zagen dat zowel in Nederland als in het Verenigd Koninkrijk dat de lage dosering (≤ 20 mg dagelijks) citalopram het meest werd voorgeschreven en het gebruik van hoge dosering (> 40 mg dagelijks) citalopram erg beperkt was over de gehele studieperiode. In beide landen daalde het gebruik van gematigde dosering (> 20 mg tot ≤ 40 mg dagelijks) citalopram significant in ouderen, nadat in 2011 de maximale aanbevolen dosering werd aangepast. Het gebruik van de hoge dosering daalde alleen significant in patiënten jonger dan 65 jaar. In beide landen waren er na oktober 2011 significant minder ouderen gestart met citalopram gebruik, dat wordt gezien als een extra, onbedoeld effect van de risico minimalisatie maatregelen.

Risico minimalisatie maatregelen en blootstelling aan geneesmiddelen tijdens de zwangerschap

Blootstelling aan geneesmiddelen met teratogene eigenschappen tijdens zwangerschap kan schadelijke effecten veroorzaken, zoals een spontane abortus of aangeboren afwijkingen bij het kind. Het zwangerschapspreventie programma (ZPP) is een aRMM dat ingezet kan worden om blootstelling aan een bepaald geneesmiddel tijdens de zwangerschap te voorkomen. In **Hoofdstuk 6** zijn de ZPP's van de zeven geneesmiddelen met elkaar vergeleken. De ZPP's van thalidomide, lenalidomide en de vitamine A derivaten (isotretinoine, alitretinoine, acitretine) zijn opgelegd gebaseerd op een vastgesteld of verwacht hoog teratogeen risico in mensen. De achterliggende reden voor het ZPP van de endothelin receptor antagonisten (bosentan en ambrisentan) is minder overtuigend. Overeenkomsten tussen de zeven ZPP's omvatten de zwangerschapstesten voorafgaand aan en tijdens het gebruik van het geneesmiddel, gebruik van anticonceptie voorafgaand, tijdens en na de behandeling, en patiëntenvoorlichting. Verschillen tussen de ZPP's omvatten het voorlichtingsmateriaal voor verschillende soorten zorgverleners, beperkte geneesmiddel uitgifte (uitgeven binnen zeven dagen na voorschrijven, maximale duur van voorschrift van 30 dagen), de periode waarna er gestopt mag worden met anticonceptie en het uitvoeren van zwangerschapstesten. Naast geneesmiddel specifieke eigenschappen dienen voorgaande ervaringen en toepasbaarheid in klinische praktijk te worden overwogen tijdens de ontwikkeling van het ZPP. Het is belangrijk om voorschrijvers, apothekers en patiënten hierin te betrekken.

In **Hoofdstuk 7** is de effectiviteit van het isotretinoine ZPP geëvalueerd door isotretinoine blootstelling in Nederlandse zwangere vrouwen tussen 1999 en 2007 te bestuderen. Met een link tussen de PHARMO database (bevat apotheek uitgifte gegevens van receptgeneesmiddelen van drie miljoen mensen in Nederland) en het geboorteregister (PRN) zijn ruim 200,000 zwangerschappen geïdentificeerd. We zagen dat 45 zwangerschappen, 2,2 (95% betrouwbaarheidsinterval (BI) 1,6 – 2,9) per 10.000 zwangerschappen, zijn blootgesteld aan isotretinoine tijdens de zwangerschap. Zestig procent van deze zwangerschappen was al zwanger op het moment dat de isotretinoine behandeling van start

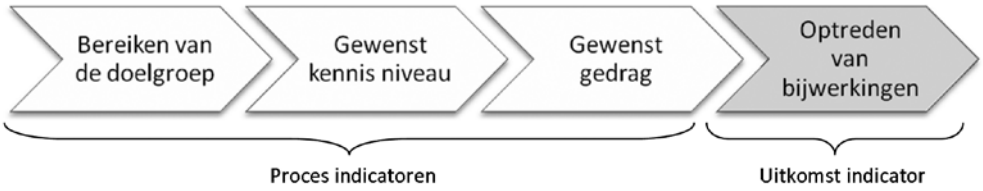
ging, wat aangeeft dat er mogelijk is afgeweken van het ZPP. Afwijkende zwangerschapsuitkomsten zoals een doodgeboren kind of aangeboren afwijkingen bij een kind waren gerapporteerd voor 9,4% (95% BI 1,3 – 17,6) van de isotretinoine blootstelde zwangerschappen. De odds ratio voor afwijkende zwangerschapsuitkomsten na isotretinoine bloostelling in de 30 dagen voorafgaand aan conceptie en tijdens de zwangerschap was 2,3 (95% BI 0,9 – 5,7). Dit betekent dat er 2,3 x zoveel kans is op een afwijkende zwangerschapsuitkomst, als er tijdens de zwangerschap isotretinoine werd gebruikt. Deze uitkomst moet voorzichtig geïnterpreteerd worden gezien de lage getallen in de analyse. Op basis van deze studie hebben we geconcludeerd dat hoewel een ZPP is geïmplementeerd sinds 1988, er nog steeds isotretinoine blootgestelde zwangerschappen voorkomen in Nederland. Ook afwijkende zwangerschapsuitkomsten mogelijk gerelateerd aan de blootstelling komen nog steeds voor. Deze bevindingen dragen bij aan het bewijs dat er geen volledige trouw is met het isotretinoine ZPP in diverse Westerse landen. Gegeven het beperkte succes van iPLEDGE, het zelfs striktere ZPP in de Verenigde Staten, is het de vraag welke maatregelen nodig zijn om de compliantie te vergroten.

Door gebruik te maken van hetzelfde cohort zwangerschappen als in Hoofdstuk 7, is in **Hoofdstuk 8** de uitgifte van geneesmiddelen met potentiële teratogene eigenschappen aan zwangere vrouwen bestudeerd. De resultaten laten zien dat in 5% van de Nederlandse zwangerschappen de vrouw een geneesmiddel met teratogene potentie ontvangt via de apotheek. In 0,7% van alle zwangerschappen betreft dit een categorie X geneesmiddel; een geneesmiddel dat niet gebruikt dient te worden tijdens de zwangerschap, omdat de mogelijke risico's duidelijke opwegen tegen de mogelijke voordelen van het geneesmiddel. Geneesmiddelen met potentiële teratogene eigenschappen dienen alleen tijdens de zwangerschap gebruikt te worden na een weloverwogen besluit waarin de mogelijke nadelige en voordelige effecten afgewogen zijn. In de toekomst kan het percentage zwangere vrouwen dat een geneesmiddel met potentiële teratogene effecten ontvangt wellicht verlaagd worden als oorzaken en redenen van gebruik van deze geneesmiddelen in kaart worden gebracht.

Meten van effectiviteit van aRMM in de dagelijkse praktijk: wat is essentieel?

aRMM hebben als doel de kans op een nadelig effect van een geneesmiddel te verkleinen of de ernst van de dit nadelige effect te verlagen. Dit proefschrift bediscussieerd de meest essentiële onderdelen die nodig zijn om de effectiviteit van aRMM in de dagelijkse klinische praktijk te evalueren. Om te beginnen moet het duidelijk zijn wat het doel van de aRMM is om vervolgens de meest geschikte uitkomstmaat, gegevensbronnen en analytische methoden vast te kunnen stellen. Er zijn verschillende stappen in het risico minimalisatie proces waar de effecten gemeten kunnen worden (zie Figuur 1). De implementatie van de aRMM in de klinische praktijk kan uitgedrukt worden in proces indicatoren: is het voorlichtingsmateriaal ontvangen, gelezen, begrepen, is er een verandering in kennis en leidt dit vervolgens tot het gewenste gedrag van de voorschrijver of patiënt. Dit zou uiteindelijk moeten leiden tot een verminderde kans op een bijwerking (de uitkomst indicator).

Figuur 1: Het risico minimalisatie proces in vier stappen



De keuze van deze verschillende uitkomstmaten (kennis niveau, voorschrijfgedrag, aantal voorgevallen bijwerkingen) om effectiviteit van de aRMM uit te drukken hangt af van het vooraf vastgestelde doel van de aRMM en de mogelijkheden tot het meten van die bepaalde uitkomstmaat. Vervolgens zijn er diverse gegevensbronnen die gebruikt kunnen worden waarin grofweg onderscheid gemaakt kan worden tussen het gebruik van bestaande databanken van elektronische patiëntendossiers (o.a. geanonimiseerde patiëntendossiers van huisartsen, apotheek uitgifte gegevens) of nieuwe data verzameling door middel van een vragenlijst of interviews. De voorkeur gaat uit naar het gebruik van bestaande databanken van elektronische patiëntendossiers gezien deze valide data bevat om gedragsindicatoren en uitkomst indicatoren te bestuderen. Bovendien is het gebruik van deze gegevensbronnen efficiënt, zodat er tijdig terugkoppeling betreffende de effectiviteit van de aRMM gegeven kan worden. Echter, niet alle benodigde gegevens om diverse proces en uitkomst indicatoren te bestuderen zijn altijd aanwezig in deze bestaande databanken. Het blijft van belang om gegevens verzameld buiten de beschikbare bestaande databanken van elektronische patiëntendossiers te gebruiken om effectiviteit van aRMM te meten hoewel het een uitdaging is dit op een efficiënte en goede manier te doen. De meest gebruikte analytische methoden om de effecten van interventies van registratieautoriteiten geïmplementeerd enige periode, nadat een geneesmiddel op de markt is gekomen te evalueren zijn de zogenoemde 'interrupted time series analysis' en de voor-na interventie analyse. Gezien aRMM vaak verplicht zijn vanaf het eerste moment dat desbetreffende geneesmiddel op de markt is, kunnen deze methoden niet altijd worden toegepast en zullen er andere mogelijke vergelijkingen gemaakt moeten worden om veranderingen of verschillen aan te kunnen tonen.

Toekomstperspectieven

Het evalueren van de effectiviteit van aRMM is een relatief nieuw onderzoeksveld waarvoor geen universeel overeengekomen standaarden en methoden beschikbaar zijn. De afgelopen jaren zijn de kennis en ervaringen over hoe de effectiviteit van aRMM geëvalueerd kan worden en de uitdagingen die hierin meespelen erg gegroeid. Het is van groot belang dat er aRMM met specifieke en duidelijke doelen worden vastgesteld en daarna dienen de meest geschikte en uitvoerbare uitkomstmaten, die de gewenste en ongewenste effecten van de aRMM in klinische praktijk weergeven, bestudeerd te worden. De kennis over effectieve aRMM is nog steeds beperkt en het is daarom van belang kennis en ervaringen over effectieve risico minimalisatie en de methodologie om dit te meten met elkaar te blijven delen. Daarnaast is er onderzoek nodig om te begrijpen wat er bereikt kan worden met aRMM in de praktijk en wanneer aRMM succesvol geacht zouden kunnen worden. Dit is belangrijk tijdens het beoordelen of aRMM nodig zijn, welk type aRMM er ingezet moet worden en het ondersteunen van de beslissing of aRMM gestopt of aangepast moet worden. De vergunninghouders en registratieautoriteiten moeten samenwerken met belanghebbenden uit de klinische praktijk (voorschrijvers, apothekers, patiënten) en het is aanbevolen gebruik te maken van relevante methoden bekend uit het 'drug utilisation' onderzoek, de farmacoepidemiologie en andere disciplines zoals gedrags- en communicatiewetenschappen.

A

APPENDICES

DANKWOORD

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Inge

LIST OF PUBLICATIONS

Zomerdijk IM, Sayed-Tabatabaei FA, Trifiro G, Blackburn SC, Sturkenboom MC, Straus SM. Risk minimization activities of centrally authorized products in the EU: a descriptive study. Drug Safety. 2012; 35(4):299-314.

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PHD PORTFOLIO

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PHD TRAINING

Research skills

2010-2012 Master of Science in Health Science, specialisation Clinical Epidemiology.
Netherlands Institute for Health Sciences, Rotterdam, the Netherlands.

Oral presentations

2011 *Risk minimisation activities of Centrally Authorised Products in the European Union: A descriptive study.*
Winter meeting Utrecht - WHO Collaborating Centre for Pharmacoepidemiology and Pharmaceutical Policy Analysis, Utrecht, the Netherlands.

2011 *The need for and feasibility of web-based educational material.*
Pharmacovigilance Working Party, European Medicines Agency, London, United Kingdom.

2011 *Hoe te meten: effectiviteit van risico minimalisatie maatregelen: een casus.*
CBG-Nefarma Workshop, the Hague, the Netherlands.

2012 *Workshop additionele risico minimalisatie maatregelen en zwangerschapspreventie programma – wanneer en waarom?*
Nationale Apothekers Dag, Ede-Wageningen, the Netherlands.

2012 *Effects of additional risk minimisation measures: what can be measured?*
Risk management colloquium 2012, Cambridge, United Kingdom.

2014 *Risico minimalisatie maatregelen en meten van effectiviteit.*
Pharmacovigilance Platform Nederland, Oss, the Netherlands.

2014 *Methodology for measuring effectiveness of risk minimisation measures.*
Pharmacovigilance Risk Assessment Committee Informal Meeting, Dubrovnik, Croatia.

2014 *Effective risk minimisation.*
FIGON Dutch Medicines Days 2014, Ede, the Netherlands.

2014 *Types of risk minimisation measures and selection of the best tools*
1st Conference Monitoring the effectiveness of risk minimisation. Drug Safety Research Unit. London, United Kingdom.

2014 *Pregnancy prevention programmes.*
1st Conference Monitoring the effectiveness of risk minimisation. Drug Safety Research Unit. London, United Kingdom.

Poster presentations

2011	*Risk minimisation activities of Centrally Authorised Products in the European Union: A descriptive study.* 23rd Annual EuroMeeting of the Drug Information Association, Genèva, Switzerland. 27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Chicago, United States.
2012	*Measurable recommendations of additional risk minimisation measures of medicinal products in the EU.* 28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Barcelona, Spain.
2013	*Dispensing of potential teratogenic drugs before and during pregnancy: a population based study.* 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Montréal, Canada.
2013	*Drug dispensing before and during pregnancy and congenital malformations: a population based study.* 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Montréal, Canada.
2013	*Methods to evaluate risk minimisation measures: a systematic review.* 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Montréal, Canada.

Courses, Seminars and Workshops

2010-2014	Research seminars in pharmacoepidemiology, department of Medical Informatics, Erasmus University Medical Center, Rotterdam, the Netherlands.
2011	Training on PSUR and RMP assessment, European Medicines Agency, London, United Kingdom.
2011-2013	Preconference courses on pharmacoepidemiology. Annual International Conferences on Pharmacoepidemiology & Therapeutic Risk Management.
2012	Biomedical English Writing and Communication, Erasmus University, Rotterdam, the Netherlands.

Other

2012-2013	Peer reviewer for Drug safety; Peer reviewer for Pharmacoepidemiology and drug safety
2012	Supervising a research project of Master student Pharmacy: Kelly Mentink, 'Evaluation methods for additional risk minimisation activities: a review', Utrecht University, the Netherlands.
2013	Provided a training course on assessment of Risk Management Plans, Thallin, Estonia.
2014	Supervising research project of Eu2P Master student: Nikica Mirošević Skvrce, 'Effectiveness of risk minimisation measures for (es) citalopram', Erasmus University Medical Center, Rotterdam, the Netherlands.

ABOUT THE AUTHOR

Inge Zomerdijk was born on 10 June 1986 in Limmen, the Netherlands. In 2004 she finished secondary school at the Jac. P. Thijsse College in Castricum and started her studies at the Vrije Universiteit in Amsterdam, the Netherlands. Inge obtained her bachelor's degree in Health Sciences in 2007. Her master's degree with specialisation International Public Health followed and as part of her training she did a research project at the department of homeless people at Psychiatrisch Centrum Suriname, located in Paramaribo, Suriname. She worked on a project to develop a programme to improve compliance to HIV therapy among HIV infected homeless people. After obtaining her master's degree in 2008, Inge started her PhD research at the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam, the Netherlands. She combined this with a part-time position as pharmacovigilance assessor at the Dutch Medicines Evaluation Board in the Hague and later in Utrecht. During this period she obtained a Master of Science in Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES). From January 2014, she works as a full-time pharmacovigilance assessor at the Dutch Medicines Evaluation Board.