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ABBREVIATIONS

ACE  Angiotensin Converting Enzyme
ADR  Adverse Drug Reaction
ARB  Angiotensin II type I blockers
ATC  Anatomical Therapeutic Chemical classification
BCPNN Bayesian Confidence Propagation Neural Network
CCB  Calcium Channel Blockers
DDD  Defined Daily Doses
ED   Erectile Dysfunction
EEA  European Economic Area
EMA  European Medicines Agency
EU   European Union
IAAAS International Agranulocytosis and Aplastic Anaemia Study
IC   Information Component
MPA  Medical Product Agency
NPC  National Pharmacovigilance Centre
PBRR Population-Based Reporting Ratio
RC   Regional Centre of Pharmacovigilance
SPC  Summary of Product Characteristics
SWEDIS Swedish Drug Information System
TdP  Torsades de Pointes
WHO  World Health Organization
UMC  Uppsala Monitoring Centre
**TERMINOLOGY**

**Adverse Drug Reaction** - A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological functions.

**Anatomical Therapeutic Chemical classification** - A classification system: the drugs are divided into different groups according to the organ or system on which they act and according to their chemical, pharmacological and therapeutic properties.

**Benefit /harm** - Benefit and harm are the positive and negative subjective, qualitative experiences of individual patients.

**Clinical trial** - A systematic study on pharmaceutical products in human subjects in order to discover or verify the effects of and/or identify any adverse reaction to investigational products.

**Defined Daily Doses** - The assumed average maintenance dose per day for a drug used for its main indication in adults.

**National pharmacovigilance centre** - A single, governmentally recognized center within a country with the clinical and scientific expertise to collect, collate, analyses and give advice on all information related to drug safety.

**Pharmacovigilance** - The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

**Population-based reporting ratio** - The total number of ADR reports collected in a safety database of a regulatory authority per year, per million inhabitants.

**Serious ADR** - Any untoward medical occurrence that at any dose resulting in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

**Signal** - Reported information on a possible causal relationship between an adverse event and a drug, the relationship being previously unknown or incompletely documented.
INTRODUCTION

Pharmacotherapy has made it possible to prevent, cure, and control many health disorders. However, no treatment involving medicines is free from the risk of harm. The harm caused by medicines can range from mild adverse drug reactions (ADRs), leaving no permanent harm, to serious, sometimes fatal reactions. Fatal ADRs have been estimated to comprise the seventh most common cause of death in Sweden resulting in 3% (3,000 deaths/year) of all deaths in the general population (1). ADRs are also a common cause of hospitalization and an economic burden (2), and more than 5% of hospital admissions has been reported to be associated with ADRs (3).

Historical background

Drug disasters have played a key role for the awareness of ADRs. The thalidomide story has served an important role in the development of drug regulation safety requirements and initiated the spontaneous reporting of ADRs globally. The system of spontaneous reporting started with the “Yellow card system” in the UK in 1964 (4).

The Thalidomide disaster

Thalidomide was first introduced to treat influenza in 1956, then as a sedative, and was subsequently introduced for nausea and vomiting during pregnancy. Chemie Grüenthal had developed thalidomide and the product was marketed under more than 60 different trade names in various countries, e.g. Contergan®, Distaval®, Kevadon®, Asmaval®, Tensival®, Valgis®, and Valgraine®. In Sweden, thalidomide was marketed as a sedative under the name Neurosedyn®. According to the drug information available at that time, Neurosedyn® was appropriate for use in pregnant women. Astra, who had the license to market the product in Sweden, started its marketing of the drug in February 1959 (5).
In November 1961, Dr Lenz contacted Chemie Grünenthal and asked the drug to be taken off the market (6). He had identified 46 women who had had babies with a limb-reduction deformity and 41 of the 46 women with deformed babies had taken thalidomide. In a control group containing 300 women, who all gave birth to children without limb abnormalities, none had taken thalidomide in the fourth to ninth weeks of gestation. The company refused, claiming that the risk was unproven. Two days later, Dr Lenz presented his findings during a pediatric conference in Düsseldorf.

In December 1961, McBride published a letter to the editor of “The Lancet” stating that children of mothers who had used thalidomide during pregnancy had an increased risk of the rare malformation phocomelia (7). He noted that 20% of the women who had ingested thalidomide during pregnancy gave birth to babies with skeletal malformations.

In this major drug disaster, approximately 10,000 children were affected and more than 150 of these were in Sweden (5). This caused a great concern about harm from drugs, and the testing of drugs in pregnant experimental animals became mandatory (8). The fact that drugs used during pregnancy could cause malformations was also the reason for establishing a spontaneous reporting system for suspected ADRs.

A regulatory problem which arose during the withdrawal of thalidomide was that the compound was marketed under many different trade names for various indications in various countries. As international collaboration in pharmacovigilance was not established at that time, the compound continued to be sold (6).

In recent years, thalidomide has been reintroduced to treat many new conditions, including human immune deficiency virus infections, skin conditions, multiple myeloma, other cancers, such as malignant melanoma and prostate cancer, and certain neurodegenerative diseases (9). However, the SPC currently includes a warning:

*Teratogenic effects*

*Thalidomide is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects.*

*Thalidomide must never be used by women who are pregnant or by women who could become pregnant unless all the conditions of the Thalidomide Celgene Pregnancy Prevention Programme are met. The conditions of the*
Pharmacovigilance

Pharmacovigilance is the science and activities related to the detection, assessment, understanding and prevention of ADRs or any other medicine-related problem (10).

The aim for pharmacovigilance is:

- To improve patient care and safety in relation to the use of medicines.
- To improve public health and safety in relation to the use of medicines.
- To contribute to the assessment of the benefits, harm, effectiveness and risk of medicines.
- To encourage safe, rational and more effective (including cost-effective) use of medicines.
- To promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

There are many important key players in pharmacovigilance: the regulatory authorities, the pharmaceutical companies, and the healthcare professionals (10). Integration of pharmacovigilance into clinical practice is needed as healthcare professionals are the major providers of case reports of suspected ADRs. Safety monitoring of medicine should be an integral part of clinical practice and the analysis of benefit/harm before initiation of a new drug is essential. When a new drug is introduced on the market, safety information is limited and is based on the results of clinical trials (11). The patients using the drugs in real life often differ from the patients in the clinical trials; they are older, the treatment diagnosis may be uncertain, they have concomitant diseases, and they are treated with other drugs. Uncommon ADRs and long term/delayed effects are seldom recognized in clinical trials due to an insufficient number of patients and no patients on long term treatment. These factors may influence the benefit/harm for the drug.
Spontaneous reporting

Spontaneous reporting is a cost effective system to follow the safety of all drugs during their entire lifecycle and also the most important source of information for regulatory actions such as taking a drug off the market or a label change due to safety problems (12-14).

Spontaneous reports are termed spontaneous as they take place during the clinician’s normal diagnostic appraisal of a patient, when the clinician is drawing the conclusion that the drug may be implicated in the causality of the event (4). The spontaneous reporting system relies on vigilant physicians and other health care professionals who not only generate a suspicion of an ADR, but also report it. To enhance patient care and safety feedback to clinical practice is important (Figure 1). In order to complete a feedback loop, information must also flow back to reporters through acknowledgement, ADR information, and bulletins describing signals.

Figure 1: The feedback loop of spontaneous reports of adverse drug reactions (ADR). Pharmacovigilance is characterised by knowledge about the safety of drugs gained from actual clinical practice where new knowledge is experienced on a practical level, that is, where it can be employed. Health care providers report ADRs to the Pharmacovigilance centre and this information is reapplied in clinical practice and, subsequently, enhances patient safety.
Internationally

World Health Organization

After the thalidomide disaster and at a World Health Organization (WHO) meeting in 1962, a network of experts from various countries was established. In 1968, a project started with six countries, of which one was Sweden, reporting spontaneous ADR to WHO.

Today, the center for the WHO's international database is situated in Uppsala, Sweden. Over 100 countries are reporting spontaneous ADRs to the Uppsala Monitoring Centre (UMC). The database contains almost eight million reports. One of the main purposes of UMC is the screening and analysis of international ADR data to detect, as early as possible, potential issues of importance for patients and public health in relation to the use and safety of medicines (15).

EudraVigilance

EudraVigilance is a data processing network and management system for reporting and evaluating suspected ADRs during the development and following the marketing authorisation of medicinal products in the European Economic Area (EEA). This database was launched in 2001. The purpose of EudraVigilance is (16):

- Electronic exchange of suspected ADR reports between the European Medicines Agency (EMA), national authorities, marketing authorisation holders, and sponsors of clinical trials in the EEA.
- Early detection of possible safety signals associated with medicinal products for human use.
- Continuous monitoring and evaluation of potential safety issues in relation to reported adverse reactions.
- Decision making process, based on a broader knowledge of the adverse reaction profile of medicinal products especially in the framework of risk management.
Sweden

In Sweden, the system for spontaneous reporting of ADRs from clinical practice was established in 1965.

According to the code of statutes of the Medical Products Agency (MPA), it became mandatory in 1975 for physicians and dentists to report fatal, otherwise serious, new and unexpected ADRs, as well as to report reactions appearing to increase in frequency. For new drugs (≤2 years on the market) all ADRs should be reported, except those labelled as common in the Summary of Product Characteristics (SPC).

In an international comparison, the reports in Sweden are considered to be of high quality. The annual number of reports has increased to around 5,000 in recent years, with about 40% comprising serious reports (Figure 2). In 2012, the National Pharmacovigilance Centre (NPC), located at the MPA, received 4,748 spontaneous reports from healthcare professionals, equivalent to approximately 500 reports per million inhabitants/year, which is a high figure in an international comparison. In a report for the European Union (EU), Sweden had the highest population-based reporting ratio (PBRR) in the EU in 2004 (17).

In spite of this, underreporting is reported to be high. In two Swedish studies, underreporting rates ranging from 86 to 100%, have been demonstrated (18, 19). A systematic review on this topic from 2006 concludes that it is not possible to provide a reliable estimate of the level of underreporting but it is likely to be in excess of 90% (20).
Figure 2: Number of reports/year in Swedish Drug Information System, 1965 to 2012. From 1998, the proportion of serious reports is indicated by lighter bars. Population in Sweden; 9.5 million in 2012.

**Regional centres and SWEDIS**

Decentralization of spontaneous reporting, with Regional Centres for Pharmacovigilance (RC), was established starting in the north of Sweden in 1992 at the Division of Clinical Pharmacology in Umeå. The purpose of this regionalization was to come closer to the healthcare practice and to increase the general interest in drugs and drug-related problems (21).

In six regional centres located at university hospitals clinical pharmacologists, specially trained nurses, and pharmacists became involved in the work with ADR reports. A clinical assessment of causality and seriousness according to WHO criteria were performed (22).

Drugs can be assessed as being suspected of having caused the reaction, as interacting with another prescribed drug, or as concomitant medication not related to the ADR. Each report can include more than one ADR and more than one suspected drug.
Information from each individual report is stored in the national database, Swedish Drug Information System (SWEDIS). The data consists of information about the patient, medications, co-morbidities, outcome, causality assessment, and administrative data. Drugs are coded according to the Anatomical Therapeutical Chemical (ATC) classification.

In addition to the work with the ADR reports, RC also had an important task to train medical and nurse students, and to inform health care professionals about ADR with a focus on the reporting of ADRs. Different activities to promote reporting are also encouraged. In the Southern Health Care Region, covering approximately 1.7 million inhabitants, RC was established in 1996. In this region the PBRR increased from 261 reports/million inhabitants in 1995 to 656 in 2011.

**Reporting form**

A special reporting form is available (Figure 3), but other methods to report are also accepted. Copies from the medical record are accepted if they include at least the minimum information requested for a report: a specific patient, a suspected drug, a suspected ADR, and an identifiable reporter. The following information is requested in the reporting form:

- name, personal identity number, and sex of the patient
- names, dosage forms, treatment dates, doses and route of administration of suspected and concomitant drugs
- relevant medical history
- seriousness and outcome of the ADR
- result of discontinuation or reintroduction

Swedish reports are often well documented and the majority include information from the medical records, results from laboratory and/or other investigations, etc. All residents in Sweden have a unique personal identity number (23), allowing the request of follow-up information if necessary.
**Biverkningsrapport från sjukvården**

För rapportering av biverkningar som har uppkommit vid behandling med läkemedel och/eller växelbaserade läkemedel eller om biverkningarna uppkommit på grund av medicineringar, missbruk, exponering i arbetet eller användning vid sidan av de villkor som angivits i produktinformationen (SPC)

OBS! Patienter/konsumenter ska rapportera biverkningar via e-ljänst eller annan blankett, se www.lakemedelsverket.se/biverknings

Alla uppgifter i rapporten behandlas med full sekreteress

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<tr>
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<td>Man</td>
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<td>Kvinna</td>
<td>Kvinna</td>
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<td>Datum då biverkningen upptäckte</td>
<td>Om patienten är gravid, ange när i graviditeten preparatet gavs</td>
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<td>Grundsjukdom</td>
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<td>Beskrivning av det inträffade (eller kopia av epikris inklusive labdata)</td>
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<td>Livshotande</td>
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<td>Aterställd med funktionsnedsättning</td>
<td>Sjukhuslängdning och förlängt sådan</td>
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<td>Okänd</td>
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<td>Okänd</td>
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<th>Advis. väg</th>
<th>Läkemedelsform</th>
<th>Dosering</th>
<th>Behandlingens varaktighet</th>
<th>Indikation (om annan än grundsjukdom)</th>
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<td>Fr.o.m</td>
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Version 2013.05.06

(1) (2)
Figure 3. The reporting form (in Swedish).
**Reporters**

According to EU Pharmacovigilance Rules, health care professionals were defined as physicians, dentists, pharmacists, nurses and coroners, at the time of the studies. The MPA had, until the beginning of 2007, defined healthcare professionals as physicians, dentists, prescribing nurses (healthcare professionals with a license to prescribe drugs), and nurses working in child and school health care. The nurses' contribution to the ADR reporting increased from 2–3% in the mid 90s to 12% in 2004 (24). Almost 90% of the drugs involved in reports from the nurses were vaccines, both for children and elderly.

There has been attempts to increase the reporting rate of ADRs by encouraging other groups of personnel in the healthcare system to report ADRs, in particular, nurses' contribution to this type of reporting (25-27). The design, aims and purposes with these studies have varied and, in some studies nurses did not have the possibility of reporting independently. A study from a geriatric clinic in the north of Sweden showed that hospital nurses, after training, could play an important role in detecting and reporting suspected ADRs (28).

Duplicate reports, i.e. cases on which both nurses and physicians report the same ADR, have been discussed in other studies (25, 27). The unique personal identity number in Sweden does not prevent duplicate reporting, but it makes it almost impossible to register ADR duplicate reports in the database.

According to data from the National Board of Health and Welfare in Sweden, nurses form the largest group of health professionals, numbering approximately 137,000, compared with approximately 40,000 physicians.

An official report initiated by the MPA, with a focus on pharmacovigilance in Sweden, suggested that all nurses should be included in the reporting scheme as an attempt to increase the reporting (29). However, the attitude among physicians regarding this and their own willingness to report, if nurses were also allowed to report, have been debated.
New rules for reporting in EU

In July 2012, new EU legislation was introduced with new rules for reporting (30). All suspected ADRs are supposed to be reported, and the definition of an ADR was changed.

Citation from
DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL:

The definition of the term ‘adverse reaction’ should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product. The suspicion of an adverse drug reaction, meaning that there is at least a reasonable possibility of there being a causal relationship between a medicinal product and an adverse event, should be sufficient reason for reporting.

It is noteworthy that reporting ADRs, when a drug is used in a manner which is not approved according to the SPC, off-label use, is highlighted in the new legislation. Off-label drug use has been associated with a potentially increased risk of ADRs. This is important in paediatric use as many drugs not are approved for use in children. In Swedish hospitals, nearly half of all prescriptions are non labelled for use in children (31).

According to the new legislation, all member states shall take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected ADR to the NPC. In Sweden, consumers were included as reporters in June 2008 and reports from pharmacists were accepted in July 2012.

In connection with the introduction of the new EU legislation, MPA decided to centralize the reporting of ADRs in July 2012. The Swedish RC task changed to focus on information and education to health care professionals and on other activities to promote reporting.
Knowledge, attitudes and incentives for reporting

The most common factors identified, in posted questionnaires, for reporting an ADR are a severe reaction and a reaction to a new drug (32-35). There are several reasons for not reporting an ADR. Among the most important factor is the fact that the reaction is already well known. Physicians (3-30%) have been found to be uncertain to report. Those studies were conducted in Italy, Germany, Sweden, and in the United Kingdom. A Spanish study showed that underreporting was selective, with a higher degree of underreporting of less severe and well known reactions (36).

Belton et al. conducted a survey in nine European countries (Denmark, France Ireland, Italy, Netherlands, Portugal Sweden, and United Kingdom) (37). The PBRR (average number of reports 1989-1993) for the participating countries varied from 9 (Portugal) to 390 (Franc) reports/million inhabitants, with Sweden on the second place with 347 reports/million inhabitants. In over 80% of the respondents in all countries, seriousness of the reaction was stated as important in the decision to report. With a larger difference between the countries, an unusual reaction or a reaction to a new drug was stated as an important factor for 60%. With a large variety from 1 to 26%, the responders stated that the reason for not reporting was that only safe drugs are marketed.

Biriell and Edwards showed that reporting was stimulated by a positive relationship between the national center and the reporter (38). They also pointed out that feedback from the national center and a simple reporting form were factors increasing overall the reporting. In studies conducted in Sweden, distribution of drug safety information has been shown to have no effect on the ADR reporting rate when the information was sent via e-mail (39). In another study, one-page ADR information was distributed to physicians and nurses but no increase in the reporting rate was noted (40). Another method tested to increase the reporting was extended feedback to reporters with relevant information from literature. No significant increase in the numbers of reports in the intervention group compared with the control group was found. However, the number of physicians reporting more than once was larger in the randomization group (41).

Another way to increase the reporting was to send a small economic inducement, in the form of two lottery tickets, to the reporting physicians (42). The difference between the numbers of reports in the
investment group compared with the control group was not statistically significant. An overwhelming majority, of the participating physicians, did not believe that this was a proper way to increase the number of reported ADRs.

Some examples on knowledge acquired from the Swedish spontaneous reporting

The spontaneous reporting system in Sweden has provided valuable information about many different perspectives on drugs. Reporting from healthcare providers has been the base for many regulatory decisions, from withdrawals to a deeper knowledge of drugs in use. Risk factors for hyponatremia in elderly patients treated with desmopressin for nocturia has been studied (43). In this analysis, spontaneous reports from both Denmark and Sweden were scrutinized showing that hyponatremia occurred during the first weeks of treatment. Interaction between tramadol and warfarine, with an increased effect of warfarine, is one example of new knowledge acquired from spontaneous reports (44). Another example is lamotrigine, an antiepileptic agent. Shortly after lamotrigine was introduced in Sweden cases of severe skin reactions associated with lamotrigine were reported (45). Four reports concerned Stevens-Johnson’s syndrome, and four cases of toxic epidermal necrolysis were reported to SWEDIS. The skin reaction appeared to be related to the rate at which the drug was introduced, and there was a recommendation to gradually escalate the dose.

Agranulocytosis
Drug-induced agranulocytosis is predominantly an idiosyncratic drug reaction on an immunological basis. Drug-induced agranulocytosis is rare, unpredictable and independent of the dose, except haematological effects of cytotoxic drugs. Agranulocytosis is defined as white blood cells <0.5x10⁹/l and a platelet count of at least 100x10⁹/l (46). Examples of drugs withdrawn from the market in Sweden due to agranulocytosis are butazones and metamizole (47).

Metamizole
The analgesic compound metamizole had been used in Sweden for several decades. In several early case reports, metamizole treatment has been linked to agranulocytosis. In Sweden, all metamizole containing products were withdrawn in 1974 due to an estimated incidence of agranulocytosis of 1 in 3,000 patients. This estimation was
based on 46 cases reported to SWEDIS, including 11 deaths, during the period 1966 to 1974 (48).

This result was in contrast with the risk estimate of agranulocytosis in a later international case-control study, the International Agranulocytosis and Aplastic Anemia study (IAAA). In this study, an excess risk of 1.1 cases per million users in a one week period was determined (49).

Due to the results of IAAA, metamizole was reapproved, in September 1995, for short-term treatment, postoperative pain and pain in connection with gall- or kidney stones, and use of the drug re-started in 1996. Due to an unexpectedly large number of ADR reports of serious blood disorders, metamizole was again withdrawn from the Swedish market in April 1999 (50). In total, 269,764 defined daily doses (DDD) of metamizole was sold in Sweden between 1996 and 1999. During this period eight reports of agranulocytosis was sent to the MPA. Although metamizole was approved for short-term treatment, seven of the reported cases had a total treatment duration of 13 days or more.

Another study conducted in the northern region of Sweden showed that metamizole was prescribed in 34% for less than one week, in 28% for 7–15 days, and in 38% for more than 15 days (51). The risks of agranulocytosis was calculated to be approximately one out of every 31,000 metamizole-treated inpatients and one of every 1,400 metamizole-treated outpatients. The higher risk estimates for agranulocytosis seen in outpatients receiving metamizole compared to inpatients is most probably related to the prolonged exposure to metamizole in outpatients.

**Sulfasalazine**

Incidence can vary over time. The estimated incidence of sulfasalazine, approved for use for inflammatory bowel diseases, induced agranulocytosis was estimated at 1/1,700 patient years. A study based on spontaneous reports of agranulocytosis considered to have a relationship with sulfasalazine showed that the incidence during the 30 first days of treatment was 1/2,400 treated patients. During the treatment period 31-90 days, the incidence increased to 1/700 treated and the risk decreased to 1/11,200 between day 91-365 (52).

The method for calculating risk over a time period with changing incidence rates is known as survival function.
Zimeldine

In March 1982, a new antidepressant drug, zimeldine, was introduced on the Swedish market. This drug had a new pharmacological mode of action, selectively blocking the reuptake of serotonin in the neurons. The advantages with this new action seemed to be fewer side effects compared with other antidepressants; moreover, zimeldine was less toxic. Clinical studies have shown that side-effects attributable to zimeldine treatment were generally of mild to moderate severity and the drug was well tolerated (53). However, suspected hypersensitivity reactions had been reported during the clinical trials.

A specific syndrome called the "zimeldine-syndrome" was reported to SWEDIS. This syndrome was dominated by fever, myalgia/arthralgia, increased liver values, headache, and exanthema. In some cases neurological symptoms also occurred and the Guillain-Barré syndrome was suspected (54).

One and a half year after the introduction, a total of 13 cases of Guillain-Barré syndrome occurred with a fairly similar relationship to zimeldine treatment, was reported. Guillain-Barré syndrome is a severe polynuropathy with motor weakness, with the annual incidence of 1-2/100,000 adults. Based on the number of DDD sold, a 25 fold increased risk for Guillain-Barré was estimated in patients treated with zimeldine, and the drug was withdrawn from the market in September 1983 (55).

Torsade de point

Torsade de point (TdP) is a rare ventricular cardiac arrhythmia characterized by periodic twisting of the points of the QRS-complexes and rates between 200 and 250 beats per minute. The incidence of TdP in the population is less than 1 in 100,000. Symptoms such as dizziness, syncope, seizures or even sudden deaths are associated with TdP. Prolongation of the QT interval, on the electrocardiogram, may predispose for TdP. Prolonged QT interval may be of congenital origin or induced by other factors such as drug use and disease. Documented risk factors for prolongation of the QT interval and TdP are old age, female gender, history of heart disease and electrolyte abnormalities such as hypokalemia and hypomagnesaemia (56).

Drugs known to prolong QT interval are antihistamines, tricyclic antidepressants, antimicrobials, antimalarial drugs, antipsychotics, and arrhythmic drugs. TdP represents an important safety issue and in the last decades, TdP has been the single most common cause of the with-
drawl or restriction of the use of drugs. Examples of drugs withdrawn from the Swedish market due to TdP: terfenadine, terodiline, thioridazine, and cisapride.

**Erectile dysfunction**

Erectile dysfunction (ED) is defined as the consistent or recurrent inability of a man to attain and/or maintain penile erection sufficient for sexual activity (57). ED is a common disorder with a reported prevalence between 13% and 46% in the general population with an exponential increase in occurrence from 60 years of age. Various medical, psychological and lifestyle factors have been implicated in the pathogenesis. Diabetes, hypertension, hyperlipidemia, obesity, smoking, and lack of physical activity are established risk factors for ED (58).

In hypertensive patients, the presence of ED is higher and the condition more severe. Treatment of hypertension with thiazide diuretics and beta blockers are known to worsen ED and in general, the calcium channel blockers (CCB), angiotensin converting enzyme (ACE)-inhibitors, and Angiotensin II type I blockers (ARB) do not worsen ED compared to placebo. Some data even suggest that sexual function and ED may improve during treatment with ARB (59).

Thus, spontaneous reporting plays an important role in terms of the knowledge of drug use in real life and there is a need for improvement of spontaneous reporting of ADRs among healthcare professionals, in general, and for nurses, in particular.
AIM OF THE THESIS

The overall aim of this thesis was to study the experiences of spontaneous reporting of ADRs by health professionals

The specific objectives of the thesis were:

- To investigate whether nurses could be a useful resource for improving the reporting rate of ADRs. Furthermore, we wanted to study how physicians working at the study departments would respond to nurses as reporters of ADRs and if the reporting by the nurses affected the reporting rate on behalf of the physicians.

- To investigate physicians’ knowledge and attitudes to and incentives for reporting ADRs in general and towards nurses as reporters of ADRs in particular in a sample of hospital physicians.

- To investigate awareness among nurses regarding their new role as reporters of ADRs in Sweden and factors that may influence reporting by nurses.

- To describe spontaneously reported cases of TdP in Sweden and to investigate if this ADR was labelled in the SPC as regards the implicated drugs.

- To study spontaneous reports of ED for different groups of antihypertensive drugs.
MATERIALS AND METHODS

Materials
Study I in this thesis was based on an educational material and a questionnaire. Studies II and III were descriptive questionnaire-based studies. In studies IV and V, individual case reports were used retrospectively (Table 1).

Table 1: Overview of the studies in the thesis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Research Questions</th>
<th>Subjects (n)</th>
<th>Method</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Oct 2003-Sept 2004</td>
<td>Whether nurses could improve reporting of ADR</td>
<td>Hospital nurses (54)</td>
<td>Education package Questionnaire</td>
<td>ADR reporting Knowledge</td>
</tr>
<tr>
<td>II</td>
<td>May 2006</td>
<td>Attitudes to ADR reporting and to nurses as reporters</td>
<td>Hospital physicians (652)</td>
<td>Questionnaire</td>
<td>Attitudes Knowledge</td>
</tr>
<tr>
<td>III</td>
<td>Sept 2010</td>
<td>Awareness attitudes toward ADR reporting</td>
<td>Nurses (453)</td>
<td>Questionnaire</td>
<td>Attitudes Knowledge</td>
</tr>
<tr>
<td>IV</td>
<td>Jan 1991-Feb 2006</td>
<td>Describe spontaneously reported cases of TdP</td>
<td>ADR case reports of TdP (88)</td>
<td>Evaluation of risk factors Review of SPC and literature</td>
<td>Labelled* Risk factors</td>
</tr>
<tr>
<td>V</td>
<td>Jan 1990-Dec 2006</td>
<td>Describe spontaneously reported cases of ED for antihypertensive drugs</td>
<td>ADR case reports of ED for antihypertensive drugs (59)</td>
<td>Evaluation of risk factors BCPNN</td>
<td>Risk factors Statistic association</td>
</tr>
</tbody>
</table>

* When the ADR was mentioned in the SPC regarding the implicated drugs
Design/methods

All studies were quantitative. Studies I, II and III were prospective, and studies IV and V were retrospective.

Three departments of internal medicine and one unit for orthopaedics were selected for a prospective study (Study I). Nurses with special drug responsibilities were invited to participate and received the educational package. The nurses were encouraged to report ADRs for a 12 month period (October 2003 to September 2004). A comparison with ADRs reported by the physicians at the study departments was made during the same period.

In order to study the participating nurses’ attitudes to, and knowledge about, ADRs and spontaneous reporting, a questionnaire was completed at the start and the end of the study. At the end of the study, a questionnaire was also handed out to all physicians at the participating departments in order to investigate their attitude towards nurses as reporters.

Studies II and III were cross-sectional questionnaire-based studies to measure attitudes and knowledge of ADR reporting. A questionnaire was sent to 1,201 randomly selected hospital physicians (Study II) and an adjusted questionnaire was sent to 753 randomly selected nurses (Study III). The nurses were selected from the 75,300 nurses who are members of the Swedish Association of Health Professionals. In both studies, the questionnaires were followed by a reminder, two weeks later. Since the questionnaire was to be answered anonymously, the second questionnaire was sent out to all recipients.

Training material

An instruction manual for reporting ADRs (Study I) and lectures in ADR reporting, definitions, classification of ADRs according to mechanisms and organ systems, pharmacokinetics, and interactions was provided. Three lectures were given at the start of the project and three lectures after six months.

Questionnaire

Different versions of the same questionnaire were used (Studies I, II, III). The questions were adapted to the category (nurses or physicians) and certain questions were added to answer specific questions for each study/category.
The questionnaire comprised four parts: demographic data (age, sex, years in profession); general questions about knowledge of pharmacology (Study III only), ADR reporting, and factors relevant to the decision to report or refrain from reporting; suggestions to improve reporting, such as electronic reporting directly via the patient’s medical records, using a simplified form, reporting without a form, reporting by phone; and interest in receiving feedback with information about the causality assessment. The answers were graded as “important/yes”, “neither/nor (neutral)”, or “unimportant/no”. At the end of the questionnaire, there was a free text area for comments.

A validation, where the questionnaire was tested on the target group, was performed before each study.

Register studies

Individual case reports of TdP reported to SWEDIS January 1991–February 2006 were identified and evaluated with regard to drug use and other possible risk factors such as female gender, heart disease, hypokalaemia and old age, over 65 years (Study IV). For the suspected drug/drugs implicated in the cases, the SPC was reviewed to find information whether TdP or QT prolongation was listed. A search was also made on the website www.torsades.org provided by University of Arizona Centre for Education and Research on Therapeutics (CERT). In addition, relevant reviews and original articles were retrieved for information.

All spontaneously reported cases of ED submitted between 1990 and 2006 to SWEDIS, where at least one antihypertensive drug was the suspected agent, were scrutinized (Study V). The groups of antihypertensive drugs were identified according to their ATC code. Patient demographics, drug treatment and ADRs were recorded. Sales figures expressed as the number of DDD for the corresponding period were obtained. The information component (IC) was calculated by using the Bayesian Confidence Propagation Neural Network (BCPNN) method.
Statistical analysis

The Statistical Package for Social Science (SPSS) was used for the statistical analysis. Chi-square testing was used to identify any significant differences. P-value<0.05 was considered as significant (Studies II, III).

We did not show the differences between proportions with 95% confidence intervals as we considered a simpler Chi-square test more appropriate and more understandable for illustrating the differences between the various groups.

BCPNN was used to calculate the strength of the statistical association between the suspected antihypertensive drugs and reported cases of ED (Study V). Large databases make the analysis of all ADRs on a case-by-case level impossible. Instead, the benefits of a large volume of data can be utilized with data-mining methods. The strength of the statistical association between a suspected drug and an ADR in a database can be calculated using the BCPNN method (Figure 4). This analysis provides a statistical indicator, the IC, to assess the disproportionality between the observed and expected number of reports, given the number of reports concerning the drug and the number of reports concerning the ADR in question (60, 61). The IC is a logarithmic measure, and a positive IC-value with a positive lower 95% confidence limit indicates a statistically significant disproportionality. The method has been found effective in identifying early drug safety signals (61).
Figure 4: Illustration of the principal of signal detection by use of Bayesian Confidence Propagation Neural Network. This analysis provides a statistical indicator to assess the disproportionality between the observed and expected number of reports, given the number of reports concerning the specific drug (x) and the number of reports concerning the specific adverse drug reaction (y) in question.

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Ethical considerations

According to the Helsinki declaration, clinical investigations must be carried out in accordance with that declaration, which implies the protection of human dignity and human life, protection of personal data, and privacy (62). Informed consent is crucial for clinical studies. In epidemiological studies, when it is impossible to identify the persons this is not necessary (63).

Study I was approved by the regional committee of research ethics in Umeå.

The questionnaire used in Studies II and III were all handled in an anonymous manner, with no possibility of identifying the responders or the non-responders. As the questionnaires were to be answered anonymously, the second questionnaire was sent out to all recipients.

In Studies VI and V, reports from SWEDIS concerning individual patients were used; however, we had only information regarding the sex and age of the patients. According to Swedish law, SWEDIS is a health data register. The purpose of health data registers is research, statistics, and the evaluation of quality of healthcare (64).
Results

Study I:
Fifty-four nurses participated in the study. During the study period, a total number of 23 reports with 39 ADRs (Table 2) were sent to the regional centers by the nurses. Seventeen (74%) of the reports were assessed as serious. Eight of the 39 ADRs were not labelled and all reports were considered appropriate according to the existing rules. At the end of the study, 86% of the nurses thought that they had sufficient knowledge to report ADRs. The reporting rate from the physicians, working at the study departments during the study period was similar to the previous year. Seven percent of the physicians stated that their willingness to report ADRs would be affected in a negative manner if also nurses were also involved in the reporting program.

Table 2: Summary of 23 cases reported to SWEDIS by nurses at three medical and one orthopedic department between October 1st 2003 and September 30th 2004.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Suspected drug(s)</th>
<th>Reported ADR</th>
<th>Labelled</th>
<th>Previously reported</th>
<th>Serious</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>F</td>
<td>ethinylestradiol and levonorgestrel</td>
<td>headache</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>unknown</td>
</tr>
<tr>
<td>73</td>
<td>M</td>
<td>zoledron rofecoxib</td>
<td>hyperkalaemia *</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>unknown</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>tramadol</td>
<td>confusion</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>recovered</td>
</tr>
<tr>
<td>91</td>
<td>F</td>
<td>warfarin ciprofloxacin</td>
<td>melaena prothrombin decreased</td>
<td>Y</td>
<td>Interaction</td>
<td>Y</td>
<td>recovered</td>
</tr>
<tr>
<td>25</td>
<td>K</td>
<td>desogestrel and ethinylestradiol</td>
<td>pulmonary embolism</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>unknown</td>
</tr>
<tr>
<td>62</td>
<td>M</td>
<td>metformin</td>
<td>anosmia ageusia body odour</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>unknown</td>
</tr>
<tr>
<td>85</td>
<td>K</td>
<td>tramadol</td>
<td>hallucinations confusion</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>recovered</td>
</tr>
<tr>
<td>86</td>
<td>K</td>
<td>lowdose salicylic acid esomeprazole clarithromycin amoxicillin lanzoprazol</td>
<td>angioedema</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>unknown</td>
</tr>
<tr>
<td>No</td>
<td>Gender</td>
<td>Drug(s)</td>
<td>Reaction(s)</td>
<td>Labelled</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>----</td>
<td>--------</td>
<td>---------</td>
<td>-------------</td>
<td>----------</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>30</td>
<td>M</td>
<td>infliximab</td>
<td>anaphylactic reaction</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>recovered</td>
</tr>
<tr>
<td>43</td>
<td>K</td>
<td>reboxetine</td>
<td>cardiomyopathy</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>unknown</td>
</tr>
<tr>
<td>84</td>
<td>M</td>
<td>cloxacillin</td>
<td>kidney failure</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>unknown</td>
</tr>
<tr>
<td>81</td>
<td>M</td>
<td>nitrofurantoin dipyridamole lowdose salicylic acid</td>
<td>ulcer duodenal anaemia</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>unknown</td>
</tr>
<tr>
<td>49</td>
<td>M</td>
<td>lisinopril</td>
<td>dizziness</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>recovered</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>lisinopril</td>
<td>dizziness cough nausea headache</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>recovered</td>
</tr>
<tr>
<td>85</td>
<td>M</td>
<td>atenolol</td>
<td>paraesthesia</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>unknown</td>
</tr>
<tr>
<td>81</td>
<td>M</td>
<td>clopidogrel</td>
<td>abdominal pain paraesthesia headache</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>unknown</td>
</tr>
<tr>
<td>68</td>
<td>M</td>
<td>tamsulosin</td>
<td>nausea nasal congestion ejaculation disorder dizziness</td>
<td>Not relevant</td>
<td>N</td>
<td>Y</td>
<td>unknown</td>
</tr>
<tr>
<td>56</td>
<td>M</td>
<td>azathioprine</td>
<td>flu-like syndrome</td>
<td>N</td>
<td>Y</td>
<td>recovered</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>K</td>
<td>isophan</td>
<td>application site reaction</td>
<td>Y</td>
<td></td>
<td></td>
<td>recovered</td>
</tr>
<tr>
<td>77</td>
<td>M</td>
<td>zolpidem</td>
<td>apnoea confusion</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>78</td>
<td>M</td>
<td>cloxacillin</td>
<td>renal failure</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>unknown</td>
</tr>
<tr>
<td>80</td>
<td>K</td>
<td>rofecoxib</td>
<td>bradycardia hyperkalaemia blood creatinine increased</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>recovered</td>
</tr>
<tr>
<td>62</td>
<td>M</td>
<td>ciprofloxacin</td>
<td>tendinitis</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>unknown</td>
</tr>
</tbody>
</table>

Abbreviations: M = male, F = female, labelled = reaction mentioned or listed in the SPC
* Hyperkalaemia was reported as an ADR to rofecoxib, however when we scrutinised the report and requested additional information, the assessment was stated as unlikely as there was a clear time relationship to another drug, zoledron.
Study II:

In total, 652 hospital physicians responded giving a total response rate of 54%. Two hundred and fifty (38%) stated that they had never reported a suspected ADR. The main factors for the decision to report an ADR were the severity of the reaction, a reaction to a new drug, and an unusual reaction (Table 3). The most important factor for refraining from reporting was that the reaction was well known. There were no significant differences between male and female or between age groups in these aspects. Sixteen percent (104) replied that they were uncertain as to how to report. In the group of no reporters, 70 (28%) were uncertain as to how to report. More than half of responders 346 (53%) stated that a web-based system for reporting would improve the reporting rate. Five hundred and eighteen (79%) stated that they would like a feedback letter containing the causality assessment. A majority were positive or neutral to nurses as reporters. Only 39 (6%) stated that their willingness to report ADRs would be affected in a negative way if nurses were involved in the reporting program.

Table 3: Hospital physicians - Factors important for determining whether to report an adverse drug reaction.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=365</td>
<td>n=276</td>
<td>n=652¹</td>
<td></td>
</tr>
<tr>
<td>The severity of the reaction</td>
<td>198 %</td>
<td>170</td>
<td>368</td>
<td>0.06</td>
</tr>
<tr>
<td>A new drug</td>
<td>205</td>
<td>157</td>
<td>362</td>
<td>0.8</td>
</tr>
<tr>
<td>Unusual reaction</td>
<td>188</td>
<td>150</td>
<td>338</td>
<td>0.4</td>
</tr>
<tr>
<td>The reaction is not labelled</td>
<td>131</td>
<td>96</td>
<td>227</td>
<td>0.7</td>
</tr>
<tr>
<td>Certainty that the reaction is</td>
<td>89</td>
<td>76</td>
<td>165</td>
<td>0.9</td>
</tr>
<tr>
<td>really due to an ADR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The reaction is labelled</td>
<td>35</td>
<td>25</td>
<td>60</td>
<td>0.8</td>
</tr>
</tbody>
</table>

¹ Those who did not state their sex are included in this total
Study III:

Of the 453 (60%) responding nurses, 265 (58%) were aware that nurses were included in the reporting of adverse drug reactions. Sixty-one nurses (14%) stated that they had reported an adverse drug reaction. Fifteen percent (n=70) of the respondents had received training about reporting adverse drug reactions (Table 4). Almost one third of these (n=21, 30%) had reported an adverse drug reaction on at least one occasion. Among nurses without training, a smaller proportion (n=40, 11%, P<0.05) had reported an ADR on at least one occasion. The two factors considered most important by nurses for reporting were the severity of the reaction and if the reaction was to a newly approved drug. Half of the nurses replied that they were uncertain of how to report and 37% had difficulties in reporting only on the basis of suspicion. A majority of the nurses (n=397, 88%) were interested in a training course in pharmacology as part of their ongoing professional development. One third (32%) of all the nurses stated that one reason for not reporting a suspected adverse drug reaction was that the responsible physician did not deem that it was necessary to report the reaction. A majority (n=380, 84%) considered that reporting a suspected ADR using a web-based system would facilitate overall reporting. Three hundred twenty-two (71%) nurses stated that they would like a feedback letter containing assessment of causalities.

Table 4: Nurses – Reporting of ADRs in relation to training about reporting.

<table>
<thead>
<tr>
<th></th>
<th>Training in reporting</th>
<th>No training in reporting</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Reported</td>
<td>21 (30)</td>
<td>40 (11)</td>
<td>61 (14)</td>
</tr>
<tr>
<td>Not reported</td>
<td>49 (70)</td>
<td>336 (89)</td>
<td>385 (86)</td>
</tr>
<tr>
<td>Total</td>
<td>70 (100)</td>
<td>376 (100)</td>
<td>446 (100)</td>
</tr>
</tbody>
</table>

P < 0.05
Study IV:

Among a total of 61,788 ADRs, 88 cases of TdP were identified. In these cases, 27 different suspected drugs were implicated. Cardiac drugs were involved in most reports (74%; 65/88), with sotalol being the most frequently suspected drug (66%, 58/88). In addition to drug treatment, two or more established risk factors were present in 85% of the cases (75/88). Heart disease (90%; 79/88) was the most common risk factor followed by age over 65 years (72%; 63/88) and female gender (70%; 62/88) (Table 5). TdP or QT prolongation was labelled in the SPC for 33% (9/27) of the drugs implicated in the 88 cases. However, supporting evidence for an association was found elsewhere in 56% (15/27) for the different drugs implicated in the reports. Although citalopram was the third most common suspected drug in the reports (10%; 9/88), TdP was not listed in the SPC.

Table 5: Distribution of risk factors, into different drug classes, other than medication in the 88 TdP cases reported to SWEDIS between January 1991 and February 2006.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Cardiac drugs* n=65 (100%)</th>
<th>Anti-depressants n=8 (100%)</th>
<th>Antibiotics n=2 (100%)</th>
<th>Several drug classes, two or more suspected drugs† n=13 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>62(95%)</td>
<td>5(62%)</td>
<td>2 (100%)</td>
<td>10(77%)</td>
</tr>
<tr>
<td>Female gender</td>
<td>47(72%)</td>
<td>6(75%)</td>
<td>2(100%)</td>
<td>7(54%)</td>
</tr>
<tr>
<td>Age over 65</td>
<td>47(72%)</td>
<td>6(75%)</td>
<td>1(50%)</td>
<td>9(69%)</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>5(8%)</td>
<td>2(25%)</td>
<td>0</td>
<td>4(30%)</td>
</tr>
</tbody>
</table>

*Drugs from Anatomical Therapeutic Chemical Classification system (ATC) class C01A, C01B, C01C, C01E and C07A.
†Antidepressants, antipsychotics, antihistamines, cardiac drugs, others
Study V:

Among a total of 225 reports of ED reported to SWEDIS 1990-2006, a total of 59 (26%) involved antihypertensive drugs, including ARB (9 cases) as suspected agents. A positive IC value was found indicating that ED was reported more often in association with antihypertensive drugs classes, except for ACE-inhibitors, compared with all other drugs in the database (Table 6).

Positive dechallenge was reported in 43 cases (73%). The median age was below 60 years except for thiazide diuretics were the median age was 65. Sixteen patients (27%) were treated with a combination from different antihypertensive drugs. In one case a beta-antagonist, as well as a thiazide diuretic was reported as suspected. Concomitant antidiabetic medication was reported in 4 out of 59 reports (7%).

Table 6: Observed and expected number of reports and corresponding IC values with 95% confidence limits, sales and reports per million DDD-years.

<table>
<thead>
<tr>
<th></th>
<th>n/Reports (expected)</th>
<th>IC value</th>
<th>IC 95% confidence limits</th>
<th>Sales (million DDD-years(^1))</th>
<th>Reports /million DDD years(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-antagonists</td>
<td>12 (2.8)</td>
<td>1.9</td>
<td>1.0 – 2.6</td>
<td>7.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>23 (4.0)</td>
<td>2.4</td>
<td>1.8 – 2.9</td>
<td>5.0</td>
<td>4.6</td>
</tr>
<tr>
<td>ACE(^2)-inhibitors</td>
<td>11 (7.1)</td>
<td>0.6</td>
<td>-0.4 – 1.3</td>
<td>5.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonists</td>
<td>9 (2.1)</td>
<td>1.9</td>
<td>0.8 – 2.7</td>
<td>1.3</td>
<td>6.7</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>5 (0.4)</td>
<td>2.7</td>
<td>1.2 – 3.7</td>
<td>1.7</td>
<td>2.9</td>
</tr>
</tbody>
</table>

\(^1\) DDD-year = 365 DDDs
\(^2\) Angiotensin Converting Enzyme
DISCUSSION

Spontaneous reporting remains a cornerstone of pharmacovigilance and is indispensable for signal detection. It is a cost-effective way of gathering information about ADRs and the information can be entered into a database as soon as it is received. This implies that is possible to retrieve and act upon ADR information without any time delay. If the system had been running during the days when thalidomide was introduced, most certainly the disaster had been discovered one and a half years earlier. The goal of pharmacovigilance must be to avoid or minimize risks with drug treatment.

This thesis shows that pharmacovigilance in healthcare plays an important role for deeper knowledge of ADRs when drugs are in use. Training was found to be one way to improve reporting; another way is to include new categories of reporters in the reporting scheme. The most important factors for reporting an ADR is the severity of the reaction and if the ADR refers to a newly approved drug. A web-based system would probably facilitate the reporting.

Reporters

Originally, physicians were the only professionals urged to report, as judging whether disease or medicine caused a certain symptom required skills in differential diagnosis. However, different categories of health professionals observe different kinds of drug related problems and by inviting reports from all professionals involved in the care of patients, it is possible to detect different kinds of ADRs and hopefully increase the reporting. Nurses have a good knowledge of the patient’s history, health status, and drug use and are well positioned to alert for ADRs (65).
In this thesis, it was revealed that nurses comprised, after training, a group of healthcare professionals that could contribute to the reporting of ADRs (Study I). The number of reports from the nurses was not extensive but the reported ADRs were all relevant. The fraction of reports regarding serious ADRs and non labelled ADRs were similar to the reports from the physicians. The number of reports from the physicians during the 12 month study period was not reduced compared with the reporting rate during the 12 month period before the study, indicating that the nurses contributed with additional reports.

In April 2007, MPA decided to accept reports from all nurses. The results from Study I contributed to the decisions to include nurses as independent reporters; earlier there was a proposal that nurses should assist the physicians in the reporting (66).

Knowledge and attitudes

In Study II, we investigated physicians’ attitudes to nurses as reporters, sending a questionnaire to 5% of all hospital physicians in Sweden. Only six percent stated that their reporting rate would be affected in a negative manner if also nurses were included in the reporting scheme. This result is in agreement with the findings in Study I; the reporting rate from the physicians did not decrease when nurses also reported ADRs. However, in Study II younger physicians were significantly more negative to nurses as reporters compared with their older colleagues.

Physicians (Study II) as well as nurses (Study III) stated that the most important factor for reporting a suspected ADR was the severity of the ADR and an ADR referring to a newly approved drug. This is in concordance with the rules for reporting in Sweden and other studies (67-69).

Inmans seven deadly sins, a theoretical model to explain the reasons for underreporting among physicians (70), include: 1) complacency, the mistaken belief that only safe drugs are allowed on the market, 2) fear of involvement in litigation, 3) guilt because harm to the patient has been caused by the treatment the doctor has prescribed, 4) ambition to collect and publish a personal series of cases, 5) ignorance of the requirements for reporting, 6) hesitance about reporting mere suspicions which might lead to ridicule, and 7) lethargy – procrastination, lack of interest or time, an inability to find a report form, etc.. A review article from 2009, based on Inmans sins, stated
that the attitudes most frequently associated with not reporting ADRs were ignorance, diffidence, and lethargy (71). The conclusion from this study was that knowledge and attitudes seem to be related to reporting and this has important implications, since knowledge and attitudes are potentially modifiable factors.

We used some of Inman’s factors for indicating non reporting in our questionnaire and adjusted the factors to, what we believe to be, a more modernized Swedish approach. The factors for non reporting for which we requested information were: 1) well known reaction, 2) uncertain how to report, 3) unaware of what to report, 4) difficulty in finding the correct form, 5) difficulties in reporting only on suspicion, 6) no need to report, 7) no time to report, 8) forgetfulness, and 9) making other priorities.

In our studies, nurses and physicians considered that reporting using a web-based system would facilitate overall reporting. In 2012, MPA introduced a web-based form for reporting and MPA are planning for a reporting system integrated in the medical records (29, 72). Of the reports 2012, 857 (18%) were submitted using the web-based system. It will be interesting to follow the progress of the use of the web-based reporting system. In the future, improved IT-based solutions with opportunities to report during routine medical practice is desirable.

When the knowledge and attitudes among nurses were studied three years after nurses were introduced as reporters, we found that more than half of the responding nurses were aware of their new role as reporters of ADRs (Study III). An interesting result was that nurses that had received training about reporting actually reported significantly more ADRs compared with those nurses who had not received any training. Thus, training seems to be associated with a high reporting frequency.

Feedback to reporters has been identified as a factor that stimulates reporting (38, 41). Feedback with information on the causality level is highly appreciated by health professionals and has an impact on the prescription habits of the reporter (73). Both physicians (Study II) and nurses (Study III) stated that they preferred a feedback letter with an assessment of the causality level between the reported ADR and the drug(s).

A problem we identified in our studies was the difficulty in reporting only on suspicion. Half of the nurses and one fourth of the physicians stated this as a factor for not reporting. This is a pedagogical problem
as reporting on suspicion is necessary to generate signals of ADRs, indicating that more training is needed.

Healthcare professionals are more likely to identify and report important ADRs if they have more knowledge in pharmacovigilance (68). Physicians have increased their ADR reporting rate 10-fold in the year following an hour long educational intervention (74). NPC and RC play a central role in this by encouraging the inclusion of the principles and methods of pharmacovigilance in healthcare. Information and education both on undergraduate and postgraduate levels in schools of medicine and nursing are essential. In this thesis it was found that education is one important means of increasing the quality and numbers of reports.

There is a general trend towards increased reporting activity according to a recently published study evaluating reporting in EU (75). This is maintained by RC and encourages reporting. Sweden had the highest PBRR in EU in 2007 and 2008. Effective communication, information, training, and flexible and uncomplicated reporting are factors identified for increased reporting.

As RC is identified as one factor for increased reporting it will be interesting to follow the progress of reporting in Sweden after centralisation of the reporting to the NPC.

Spontaneous reporting

The reporting from the nurses has not increased after nurses were included as reporters. In 2004, a total of 12% of the reports were submitted by nurses (24), and in 2011 a total of 13% of the reports was submitted by nurses. Two percent of all reports in 2011 were submitted by hospital nurses. It takes time to include a new category of reporters. In Italy, where nurses have been involved by law in reporting ADRs since 2003, the reporting is still low. However, the number of reports from nurses has started to increase (76). In the UK, nurses contributed to over 20% of the reports according to the annual statistics for 2010/2011 (77).

The reporting in Sweden has stagnated during recent years (Figure 2). In 2009, the number of reports was at an all-time high due to a vaccination campaign against pandemic flu - Influenza A (H1N1). In Sweden, 60% of the inhabitants were vaccinated. An urgent request was sent to Swedish healthcare providers to report ADR, and for the
first time it was possible to report electronically. Altogether, 2,521 reports related to the pandemic flu were submitted.

Among the Pandemrix (a vaccine against the influenza A (H1N1)), reports of signals of narcolepsy was identified in August 2010. These signals have been investigated and the risk of narcolepsy in the age group of 4–19 years was 4-fold among those Pandemrix-vaccinated in comparison with those unvaccinated in the same age group. The narcolepsy signal has resulted in many question marks as the elevated risk for narcolepsy has only been observed in Sweden, Finland and Island and not in the other countries in EU using the same vaccine. The association between narcolepsy and Pandemrix vaccine requires further investigation (78). A register study covering over 60% of the Swedish populations confirm the previous result, however in this study, the risk was 3-fold among those vaccinated below 20 years of age. In this study an increased risk for narcolepsy in the age group of 21-30 years have also been found (79).

**Torsade de pointes**

Another signal from spontaneous reports is TdP in connection with use of citalopram (study IV). Citalopram was implicated in 9 out of 88 TdP cases as a suspected drug, during the study period of 15 years. In addition, citalopram also occurred as concomitant medication in five reports. TdP or QT prolongation was not listed in the SPC (valid September 2006) or mentioned in the reference literature.

Study IV was cited in a publication evaluating TdP reported to the Food and Drug Administration (FDA) in the US. In this study, 12 cases of TdP for citalopram were identified. (80). In the discussion it was stated:

> Notably, in a recent issue of this journal, Åström-Lilja et al reported nine cases of citalopram-induced TdP to the Swedish pharmacovigilance database. Although a real risk is doubtful at recommended doses, the occurrence of TdP should be taken into account in patients experiencing overdose, as recognized in the label.

In October 2011, a dear doctor letter was posted from the pharmaceutical company (Lundbeck Sverige) in cooperation with MPA (81). The letter stated:
Citalopram causes dose-dependent QT interval prolongation.
Citalopram should no longer be prescribed in doses over 40 mg per day.
20 mg per day is the maximum recommended dose for patients with hepatic impairment and elderly patients.
Citalopram should not be used in patients with congenital long QT syndrome.
Use of citalopram together with other drugs that are known to prolong QT interval is contraindicated.
Patients with congestive heart failure, bradyarrhythmias, or predisposition to hypokalemia or hypomagnesaemia because of concomitant illness or drugs, are at higher menace of developing torsade de pointes.

The restriction was based on a randomized, multi-centre, double-blind, placebo-controlled, crossover study (119 subjects) (unpublished) and data from spontaneous reports (82). This highlights the importance of spontaneous reporting of previously unknown reactions to generate signals of new ADRs.

In a publication, after the dear doctor letter was published, the warning was criticised. The authors stated that the restriction was not placed in the context of either benefits or risks in real-world clinical practice. In the publication they refer to our study (82):

Åström-Lilja et al. searched a national Swedish database covering January 1, 1991 to February 1, 2006 (about 15 years and 61,788 adverse drug reactions) for drug-induced torsade de pointes. They found 101 suspected cases of drug-induced torsade de pointes, of which 5 died (2 were considered to have died from torsade de pointes). Of 88 eligible cases involving 116 drugs, citalopram was implicated in 9 cases and occurred as a concomitant drug in an additional 5 reports. They concluded that citalopram needed further investigations to better define any association with torsade de pointes.

The recommendation in this publication was to publish case reports of psychototropic drug-induced QT prolongation, TdP, and sudden cardiac death. The purpose was that clinicians and investigators would better understand the clinical implications of prescribing such drugs as citalopram.
Erectile dysfunction

As the risk to develop ED increases with age, it is noteworthy that the patients described in the reports were quite young (Study V). Another surprising observation was that a concomitant antidiabetic medication was reported in only 4 out of 59 reports (7%). This might reflect a reporting bias in terms of an increased willingness to report ED if other risk factors such as high age or diabetes, are absent.

There was a statistically significant IC-value for all groups of antihypertensive drugs, except ACE-inhibitors, indicating a higher than expected reporting rate of ED for these drugs. This is an interesting finding in view of results from other studies suggesting a positive effect of ARB on ED. With the exception for irbesartan (Aprovel®; Sanofi-Aventis), ED is not listed in the SPC for ARBs and this may affect the willingness to report suspected ED for ARBs in accordance with the rules for reporting in Sweden, to report unexpected ADRs. Moreover, there is also a possibility that ARBs are prescribed selectively to men with a probability of developing ED.

ACE-inhibitors, ARB and CCB are reported in observational studies to have no relevant or even positive effects on ED (83). For drugs acting over the renin-angiotensin system there are indication of beneficial effects (84), in line with experimental studies showing improved endothelial and erectile function. Large clinical trials specifically evaluating the role of antihypertensive drugs on the sexual function do not exist (85). However, results from clinical trials have shown that treatment with ARB; (telmisartan) and/or ACE-inhibitors (ramipril) did not ameliorate erectile dysfunction in high-risk patients with preexisting erectile dysfunction. However, the treatment did not prevent new-onset of erectile dysfunction in these patients.

The relatively high reporting of ED in association with ARB in our study is in contrast with other studies suggesting that ARB has no, or a positive effect, on ED. This discrepancy suggests that further studies are warranted on this potential adverse reaction to ARB.
Other considerations

Denominator
Choice of an appropriate denominator when evaluating pharmacovigilance data is difficult. Sales figures expressed as the number of DDD were used for assessing spontaneous reporting rates (Study V). A more relevant denominator is the number of treated individuals. This information can now be obtained from the Swedish Prescribed Drug Register, a national healthcare register on dispensed pharmaceuticals (86). This denominator has been used to evaluate the extent of the ADR reporting in children (87).

Coding ADRs
The national board of health and welfare in Sweden provides guidance on coding diagnoses in clinical practise in accordance with International Statistical Classification of Diseases and Related Health Problems (ICD) - Tenth Revision. The recommendation is to use an ICD code of drug associated problems when an ADR is suspected (88). One way to code an ADR is to use Y57.9 (adverse effects in the therapeutic use of drug or medicament unspecified) together with the ATC code for the suspected drug/drugs and the ICD code for the signs and symptoms of the ADR. If this coding is used, it can be a trigger for reporting and increase the awareness of suspected ADRs (89). Today ADRs are not always documented in the patients’ medical records (90).

National drug strategy
A national drug strategy, was posted by the government in 2011 (91). The goal was to secure world class safety for the patients. The need of systematic follow-up of new drugs with a focus on efficiency and safety was emphasised. Groups of particular interest in terms of follow-up were the elderly, patients with multiple diseases, and children.

An excerpt from the report:

Reporting of adverse drug reactions is an important base to detect inconsistencies in the handling of drugs and increase drug safety. There is a need for more flexible and user-friendly reporting of ADRs e.g., reporting directly from the patients’ medical record, to motivate and stimulate increased ADR reporting and feedback of knowledge for increased patient safety.
The results from this thesis are in accordance with this strategy. Improved training about drugs and drug use for physicians is also highlighted in the strategy. The knowledge acquired during university studies provides important information. Training in pharmacovigilance varies significantly and continuing medical education is important in providing up-to-date information and knowledge (92). The way training and examinations in clinical pharmacology in medical school are currently managed in Sweden today, with integration of this speciality into the courses covering other specialities, may have negative consequences on pharmacology knowledge (93).
Limitations

In these studies, there are certain weaknesses in the methods used.

Selection bias
As a random sample of all hospital physicians was selected in Study II, it was not probable that selection bias would take place. The physicians represented all hospital physicians in Sweden.

In Study III, a membership register from the trade union, the Swedish Association of Health Professionals was used to obtain addresses. Every hundredth nurse was selected from an alphabetical list of the membership register. There are some limitations with this approach, because we had no information regarding nurses who were not members of the union. However, this was the only way to obtain access to an address register for nurses in Sweden, and the overall membership is high, including at least 50% of nurses in Sweden. It is possible that the nurses that are members of the union have a greater knowledge and awareness about ADRs and reporting compared with their colleagues that not are members of the union.

Non responders
The response rate in Studies II and III was reasonable and similar to other studies (32, 33). However, we do not have any information from the non-responders to the questionnaire. This affects the generalizability of the results. One could assume that the responders are interested in ADRs to a higher degree and have a greater awareness about reporting compared with non-responders. Thus, there might be some overestimation of the results.

Questionnaire
Different versions of the same questionnaire were used in Studies I, II and III. An almost identical questionnaire has been used before investigating physicians attitudes to reporting (32). However the questionnaire was not standardized. A pilot study of the questionnaire was performed on a target group before each study.

The answers were ranked in three levels “important/yes”, “neither/nor (neutral)”, or “unimportant/no”. This is a simplified version of the 5-point Linkert scale, used in previously conducted surveys where the ranking corresponds to five alternatives; 1=completely disagree, 2=disagree, 3=moderately agree, 4=agree, and 5=completely agree (94).
Internal loss

Missing data for the different questions ranged from 2% to 41%. This may have affected the results and contributed to overestimation of those results. However, in the questionnaire, not all alternatives were meant to be responded to. It was stated in the questionnaire that several alternatives may be valid.

Reporting bias

Studies IV and V are based on spontaneous reporting. A number of limitations should be acknowledged when interpreting data from spontaneous reporting systems. Information in the reports is often incomplete making it difficult or impossible to establish causal relationships between the reported event and the drug. Moreover, there is a substantial underreporting of adverse events and the reporting is not homogenous (36). The reporting rate is affected by numerous factors. The severity of the reaction, whether the reaction is a labelled ADR, and if the reaction is associated with a newly launched drug, have been identified as important factors in determining whether or not to report an ADR (37).

TdP is very specific rare diagnoses associated with drugs and this will probably increase the reporting rate (46). There has also been a focus on drug related TdP during the last decades (56). ED is common in the population and can be difficult to identify as an ADR. In addition, admitting ED in a consultation with the physician can be difficult (95), and even if the patient discusses ED with his physician there is probably a great deal of underreporting. Another complicating factor is that the indication for treatment, hypertension, is a cardiovascular risk factor which is significantly associated with ED (96). In this study, treatment with anti-diabetic drugs was used as a surrogate variable for diabetes.
Implications and future work

Healthcare professionals and patients are the starting point and ending point of pharmacovigilance (Figure 1). Spontaneous reporting of suspected ADRs from healthcare professionals remains 50 years after the thalidomide disaster the main source for new signals of ADRs.

When ADRs appear – particularly previously unknown in association with the medicine – it is essential that the information should be analyzed and communicated effectively. This is an important role of pharmacovigilance.

There are many examples from lessons learned from spontaneous reporting. Metamizole, when reintroduced for short term use on the Swedish market, was, again, withdrawn due to agranulocytosis. An analysis of the reported ADRs was performed, but no obvious risk group was found. However, metamizole was not used according to the SPC and in seven of the eight reported cases of agranulocytosis the treatment duration was 13 days or longer. This demonstrates the problem when a drug is not used in concordance with the SPC. For sulfasalazine spontaneous reports were used to estimate the risk of agranulocytosis in relation to treatment time, the survival function. As sulfasalazine is for long term use, this is important knowledge for both physicians and patients and should be considered in the benefit/harm assessment. In this case the traditional expressions of risk underestimate the risk for the individual patient. Zimeldine was the first drug in a new class of antidepressants. It was marked as an non toxic drug with few ADRs, but after only one and a half years on the market zimeldine was withdrawn due to serious ADRs raised during clinical practice.

An ongoing signal, developed from the spontaneous reporting, is narcolepsy after vaccination with Pandemrix. This is a good example of an unusual serious ADR that not can be detected in clinical trials due to a limited numbers of patients and short term follow up. The signal was initiated by a vigilant physician sending reports to the RC in the Southern Health Care Region; there are currently (January 2013) more than 200 reports in SWEDIS.

TdP and ED are totally different ADRs that have been studied in this thesis. ED is highly prevalent and has impacts on the overall health of sexually active men, and poor adherence to antihypertensive drug therapy due to ED has been discussed (85). TdP is a significant life
threatening ADR and has been one of the most common causes of restriction or withdrawal of drugs. In our Study IV, we found that citalopram was reported as a suspected drug; however, neither QT prolongation, nor TdP, was labelled in the SPC. Three and a half years after our publication a restriction on the use of citalopram was posted due to QT interval prolongation.

Healthcare professionals’ willingness to detect and report ADRs is important to patients’ safety. Hopefully, expansion of the reporting groups will facilitate overall reporting. All nurses in Sweden were included as reporters in 2007 (29); this decision was partly based on Study I in this thesis. When including a new group of reporters it is important that the reporting rate from other groups of healthcare professionals not decrease. We confirmed that the reporting rate from the physicians would not decrease if nurses were included as reporters (Studies I, II).

Investigation of physicians and nurses knowledge and attitudes (Studies II, III) towards reporting is a means of improving both the quality and the quantity of the reports. To highlight health professionals’ concerns about possible ADRs is a way of developing a new hypothesis on safety issues. Improved IT solutions to record information on suspected ADRs during routine clinical practice are essential to increase the reporting of suspected ADRs. Development of mechanisms for the automatic, systematic capture of health professional ADR suspicions is an issue for the future (97). Improved information and education is needed to secure safer treatment with drugs.

In the future, it would be worthwhile to study:

- Effects of web-based spontaneous reporting of ADRs and other user friendly ways to report e.g. integrated reporting in the patients’ medical record.
- Effects on reporting and awareness of ADRs after training all groups of healthcare professionals.
- Effects on reporting after centralisation of the reporting.
- Ways to communicate pharmacovigilance information in a manner that improves therapeutics.
SUMMARY AND CONCLUSIONS

Spontaneous reporting of ADRs from health professionals is important for detection of signals indicating new ADRs. The spontaneous reporting could be improved if new categories of healthcare providers are included as reporters. Information and training could improve the reporting. A web-based system for reporting will facilitate the reporting.

From this thesis it is concluded that:

- Introducing and educating nurses as reporters of suspected ADRs is important not only for obtaining and receiving additional reports of ADRs, but also for disseminating knowledge about drugs and drug-related problems. Adverse drug reaction reporting by nurses could improve the overall safety of drugs (Study I).

- Hospital physicians regard the severity of the reaction to be the most important factor in reporting an ADR. Underreporting could be reduced if a web-based system for reporting is introduced. Inclusion of hospital nurses as reporters will not decrease the reporting rate of physicians (Study II).

- More than half of the study population of nurses were aware of their new role as reporters of adverse drug reactions, but few of the responding nurses had reported an adverse drug reaction. Given that training seems to be associated with a high reporting frequency, we suggest more training in pharmacovigilance for nurses (Study III).
• TdP is a rarely reported ADR. Several risk factors are often present. In two thirds of the drugs implicated in the reports, neither TdP nor QT prolongation was labelled in the SPC. Further investigations are needed regarding the association between citalopram and TdP (Study IV).

• All classes of major antihypertensive drugs including ARB were implicated as suspected agents in spontaneously reported cases of ED. The relatively high reporting of ED in association with ARB is in contrast with previous studies suggesting that ARB have no or a positive effect on ED. This discrepancy suggests that further studies are warranted on this potential adverse reaction to ARB (Study V).
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