An adverse drug event manager facilitates spontaneous reporting of adverse drug reactions

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ABSTRACT

INTRODUCTION: Spontaneous reporting of adverse drug reactions (ADRs) is used for continuous risk-benefit evaluation of marketed pharmaceutical products and for signal detection. The Adverse Drug Event Manager (ADEM) is a service offered to clinicians employed at hospitals in the Capital Region of Denmark. The ADEM assists healthcare professionals in reporting suspected ADRs to the Danish Health Authority. The aim of this retrospective observational study was to quantify and describe ADRs reported via the ADEM in 2014.

METHODS: All ADR reports handled by the ADEM in 2014 were recorded anonymously and analysed descriptively.

RESULTS: A total of 484 ADRs were reported through the ADEM in 2014 (the median number of reports per month was 37; range: 17-78). The majority of the reports came from departments of internal medicine (61%), psychiatry (14%) and dermatology, ophthalmology or otorhinolaryngology (11%). The drugs most frequently reported were lisdexamphetamine (n = 40), rivaroxaban (n = 16) and warfarin (n = 15) (vaccines excluded). In 13 out of 484 reports, the ADR was associated with a fatal outcome.

CONCLUSION: The findings of this study indicate that an ADEM promotes and facilitates spontaneous ADR reporting and helps raise awareness about ADRs, including how and why they should be reported. Hopefully, this will assist national and European spontaneous reporting systems in their work to increase patient safety nationally and abroad.

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Spontaneous reporting of adverse drug reactions (ADRs) is an important part of post-marketing drug surveillance and, in a broader perspective, a means of improving patient safety. ADR reporting is used for safety signal detection and continuous risk-benefit evaluation of marketed pharmaceutical products.

In Denmark, physicians, dentists, midwives and veterinarians are obliged by law to report the following types of ADRs to the health authorities [1]:

- Unexpected ADRs (those not listed in the summary of product characteristics)
- Serious ADRs:
  - Fatal or life-threatening
  - Leading to hospitalisation (initial or prolonged)
  - Leading to disability or permanent damage
  - Leading to congenital malformations
- ADRs caused by drugs under stricter reporting requirements (i.e. marketed within the past two years)

Underreporting of ADRs is a major healthcare challenge, both in in Denmark and internationally [2]. Underreporting is due to healthcare professionals' limited knowledge about available reporting systems and about the types of ADRs that should be reported. Moreover, indifference, diffidence and lack of time also seem to play a role [2-4].

The Capital Region of Denmark (1.8 million inhabitants) decided to establish an Adverse Drug Event Manager (ADEM) to facilitate reporting of adverse drug events. An adverse drug event is any injury experienced by a patient who is in treatment with a drug that is not necessarily causally related to the treatment. An ADR is a type of ADE in which a causative relationship is suspected. During the pilot phase (October 2010-September 2011), the ADEM only received reports on ADRs. It was established as an offer for the whole region in January 2013 and it was then decided that the ADEM would only receive reports of ADRs, whilst still keeping the function's name [5]. The ADEM is located at the Department of Clinical Pharmacology at Bispebjerg and Frederiksberg Hospital. The ambition was to make the administrative process needed for ADR reporting less time-consuming than previously for physicians employed at the hospitals in the Capital Region of Denmark. Another important aspect of the ADEM is to raise awareness about ADRs and why it is important to report them through education of and information to healthcare professionals [5, 6].

The aim of this retrospective observational study was to quantify and describe ADRs reported via the ADEM in 2014 in an effort to provide data to discuss the value and impact of the established ADEM function.

ORIGINAL ARTICLE

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TABLE 1

The number of adverse drug reactions classified according to the Medical Dictionary for Regulatory Activities, by System Organ Class.

Reaction according to System Organ Class	n
Nervous system disorders	267
General disorders and administration site conditions	247
Gastrointestinal disorders	219
Skin and subcutaneous tissue disorders	148
Respiratory, thoracic and mediastinal disorders	110
Psychiatric disorders	102
Musculoskeletal and connective tissue disorders	76
Investigations	59
Blood and lymphatic system disorders	56
Eye disorders	52
Injury, poisoning and procedural complications	51
Renal and urinary disorders	43
Vascular disorders	31

TABLE 2

The number of adverse drug reaction (ADR) reports per hospital: absolute numbers and relative to the number of bed-days.

Hospital[a]	ADR reports, n	Per 10,000 bed-days
Bispebjerg/Frederiksberg Hospital	175	8.37
Gentofte Hospital	58	7.96
Glostrup Hospital	26	2.67
Mental Health Services, Capital Region of Denmark	69	1.83
Herlev Hospital	46	1.76
Hvidovre/Amager Hospital	36	1.41
Bornholm Hospital	4	1.25
Rigshospitalet	45	1.24
North Zealand Hospital	25	0.95
Total	484	2.50

a) Hospital structure in the Capital Region of Denmark as of 2014.

TABLE 3

The most frequently reported drugs.

Drug	ATC code	Reports, n
Lisdexamphetamine[a]	N06BA12	40
Vaccine[b]	-	19
Rivaroxaban	B01AF01	16
Warfarin	B01AA03	15
Bendroflumethiazide with potassium chloride	C03AB01	15
Spironolactone	C03DA01	11
Phenoxymethylpenicillin	J01CE02	10
Acetylsalicylic acid	B01AC06	10
Dabigatran etexilate	B01AE07	9
Ibuprofen	M01AE01	9
Aripiprazole	N05AX12	7
Zoledronic acid	M05BA08	7
Metformin	A10BA02	7
Nitrofurantoin	J01XE01	7
Infliximab	L04AB02	7

ATC = Anatomical Therapeutic Chemical Classification System.
a) 38 reports came from a single neuro-paediatrician.
b) Diphtheria-*Haemophilus influenzae*-pertussis-polio-tetanus vaccine.

TABLE 4

Fatal adverse drug reactions and suspected causal drugs.

Suspected drug	Reported cause of death
Acetylsalicylic acid	Cerebral haemorrhage
Atorvastatin	Shock, multi-organ failure
Dabigatran etexilate	Cardiac arrest
Hydroxyzine	Toxic epidermal necrolysis, sepsis
Levetiracetam	Toxic epidermal necrolysis, sepsis
Metformin	Cardiac arrest
Nitrofurantoin	Pulmonary fibrosis leading to respiratory failure
Nitrofurantoin	Respiratory failure
Pirfenidon	Malaise[a]
Rivaroxaban	Cerebral haemorrhage
Warfarin	Cerebral haemorrhage
Warfarin	Cerebral haemorrhage
Zoledronic acid	Respiratory failure, ventricular fibrillation

a) No other, more serious, symptoms were reported.

METHODS

All ADRs handled by and reported through the ADEM in 2014 were included in this study. Every included ADR was reported to the ADEM by a physician affiliated with a hospital in the Capital Region of Denmark. The physician contacted the ADEM (a first-year resident in clinical pharmacology) by phone, fax or e-mail.

As a minimum the physician provided information about their affiliation, the patient's initials and personal identification number, the suspected drug(s) and the ADR(s).

By using the patient's electronic medical record, which includes prescribed and administered drugs, lab results, X-rays, etc., the ADEM handled the actual reporting to the Danish Health Authority (DHA), using their electronic reporting form [7].

Each ADR report contained information about the suspected reaction(s) and severity as well as about the healthcare professional who contacted the ADEM (position, department, hospital), the patient (age, sex, comorbidities, medication), the suspected drug (indication, formulation, dosage) and the name of the ADEM physician.

Only ADR reports that were received and confirmed by the DHA were considered for the present analyses. Data on all ADRs were handled and analysed using Microsoft Access 2010 and Microsoft Excel 2010. Data were analysed using descriptive statistics. Each ADR included in each report was categorised according to the Medical Dictionary for Regulatory Activities [8] (**Table** 1). The project was approved by the Danish Data Protection Agency.

Trial registration: not relevant.

RESULTS

In 2014, a total of 484 ADRs were reported through the ADEM. The median number of reports handled by the ADEM was 37 per month (range: 17-78) (**Figure 1**).

Reporter characteristics

The ADEM received reports from all hospitals in the Capital Region of Denmark. **Table 2** shows the number of reports per hospital, absolute and relative to the number of bed-days (as an indication of hospital activity).

The affiliation and/or specialty of the reporting physician was distributed as follows: 61% were from a department of internal medicine, 14% from a psychiatric department, 11% from a department of dermatology, ophthalmology or otorhinolaryngology, 7% from a department of surgery, 4% from a paediatric department, 2% from an emergency department and 1% was from a department of obstetrics/gynaecology.

Patients with a suspected ADR had a median age of 58 years (range: 0-97 years), and 59% were female.

The reports concerned 285 unique drugs. The most frequently reported drugs are shown in **Table 3**.

Each report could contain several ADRs. For instance, there were 40 reports on lisdexamphetamine with 95 specified ADRs (cf. Table 3). This means that each filed report contained more than one ADR related to the drug. For lisdexamphetamine, the symptoms most frequently reported were changes in either appetite/weight (n = 31), mood (n = 22) or sleep patterns (n = 12).

The total number of adverse reactions reported for rivaroxaban was 56; 18 were related to bleeding, and ten concerned symptoms from the gastrointestinal system (not related to bleeding). Among the remaining reported ADRs were abnormal blood pressure (n = 5), rash (n = 4), dyspnoea (n = 3) and Henoch-Schonlein purpura nephritis (n = 2).

For warfarin, cerebral haemorrhage/infarct was the most frequently reported ADR (n = 16), followed by other symptoms related to the nervous system (n = 15).

The total number of ADRs listed in the 484 reports was 1,461. Overall, the most frequently reported symptoms were nausea (n = 37), decreased appetite (n = 33) and dyspnoea (n = 32).

Of the 484 reports, 64 concerned drugs under stricter reporting requirements (no fatal outcomes).

The proportion of fatal ADRs was 13/484 (2.7%) (**Table 4**). In four of these cases, the suspected drug was an anticoagulant. Cerebral bleeding was the ADR reported in three cases. Two fatal events were caused by nitrofurantoin due to respiratory failure.

DISCUSSION

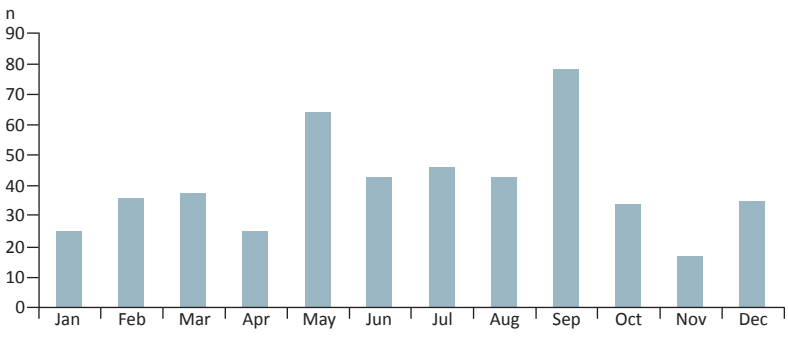
In this retrospective observational study, we quantify and describe ADRs reported in 2014 through the ADEM, a service offered to physicians employed at hospitals in the Capital Region of Denmark. A total of 484 ADRs were reported, and the majority of the reports came from departments of internal medicine, psychiatry and dermatology, ophthalmology or otorhinolaryngology. Excluding vaccines, the drugs most frequently reported were lisdexamphetamine, rivaroxaban and warfarin. In 13 out of 484 reports, the ADR was associated with a fatal outcome.

Although absolute quantities were small, the number of reports received from individual hospitals differed considerably, with healthcare professionals employed at one particular hospital (Bispebjerg and Frederiksberg Hospital (BFH)) reporting more frequently than others (Table 2). In addition to physical proximity (the ADEM is located at the BFH), all new employees at the BFH are introduced to the ADEM and all heads of department are encouraged to report ADRs to the ADEM. This underlines the importance of leadership, visibility and proximity in increasing the number of spontaneous ADR reports [3, 5, 6].

As expected, the majority (61%) of ADR reports came from departments of internal medicine. However, it is noteworthy that some specialties/departments reported few, if any, ADRs. Spontaneous reporting seems to be highly dependent on individual healthcare professionals and their knowledge, motivation and dedication [3]. To take an example, 38 of 40 ADRs suspected to be caused by lisdexamphetamine were reported by a single neuro-paediatrician [9]. Similarly, the ADEM received a relatively large number of reports on the diphtheria-*Haemophilus influenzae*-pertussis-polio-tetanus vaccine (Table 3). These reports came from a single allergy and dermatology department with focus on granuloma at the injection site and allergy to metals after immunisation. Although reporting of these specific ADRs is not

FIGURE 1

Number of adverse events reported through the Adverse Drug Event Manager in 2014 (monthly distribution).



mandatory according to Danish legislation, the reports are, indeed, valuable. They contribute to the evaluation of the actual incidence of known ADRs in a post-marketing setting, allowing for, e.g., risk estimation and financial analyses of their impact.

Excluding lisdexamfetamine and vaccines, the two most frequently reported drugs causing an ADR were rivaroxaban and warfarin. This is not surprising as earlier studies have shown that anticoagulants and antiplatelet drugs are among the drugs most commonly associated with ADR-related hospitalisations [10-12]. Accordingly, five of the ten most frequently reported drugs in this study were antiplatelet drugs or anticoagulants (cf. Table 3). Moreover, these drugs were the suspected agent in four out of the thirteen fatal ADRs reported to the ADEM.

The ADEM received relatively few reports on drugs that were under stricter reporting requirements (i.e. marketed within the past two years). In 2014, a total of 123 drugs were classified as such by the DHA, but the ADEM only received 64 reports on eleven different drugs. In order to assess post-marketing drug safety, it is mandatory to report *any* ADR suspected to be caused by these drugs. It is possible that many healthcare professionals are unaware of this legal obligation, and we believe that the actual number of ADRs caused by newly marketed drugs is much larger than indicated by our results.

Two of the fatal ADRs were suspected to be caused by nitrofurantoin used in the long-term treatment and prevention of urinary tract infections and leading to irreversible pulmonary fibrosis and ultimately respiratory failure and death. After receiving these two reports, the ADEM initiated collaboration with experts from relevant fields, including the DHA, and (re)informed general practitioners about this known adverse effect of this antimicrobial agent. This illustrates the ADEM's ability to facilitate drug-safety signal detection and its role in educating and informing the relevant parties in the healthcare system.

The ADEM was formally launched in January 2013, so it is still somewhat early to fully evaluate the function's contribution to signal detection and, ultimately, to improving patient safety. We do, however, believe that the ADEM has potential to increase both the quantity and quality of ADR reports. The number of ADRs reported through the ADEM was 345 in 2013 and thus lower than in 2014 [13]. With respect to the total number of ADR reports received by the DHA from hospitals in the Capital Region of Denmark, the ADEM handled a relatively larger proportion in 2014 than in 2013 (345/627 (55%) in 2013 versus 484/710 (68%) in 2014). The quality of the ADEM's ADR reports, which are sent to the DHA, has not been established, but it seems advantageous that reports are made by physicians who have the time, knowledge and professional enthusiasm to do a comprehensive report. The ADEM physicians exchange ideas and experiences continuously and in close collaboration with the DHA. It might be a theoretical disadvantage that the ADEM does not have the direct patient contact, as important clinical information might be lost. However, the ADEM has full access to the patients' comprehensive electronic records, including laboratory values and prescribed drugs.

CONCLUSION

Spontaneous reporting of adverse drug events is essential for post-marketing evaluation of safety profiles of drugs in a "real life" setting. However, underreporting is a major challenge. In the Capital Region of Denmark, we conclude that the establishment of an ADEM seems to have contributed to an increase in the number of ADR reports, and we believe that the ADEM fills an important role by qualifying ADR reporting. Although absolute numbers are still small, and longer follow-up is needed to fully evaluate the function's potential, the findings of this study strongly indicate that an ADEM promotes and facilitates spontaneous ADR reporting. By informing and giving feedback to healthcare professionals and other relevant parties, the ADEM helps raise awareness about ADRs, including how and why they should be reported. Hopefully, this will assist national and European spontaneous reporting systems in their work to increase patient safety nationally and abroad.

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