Evidence Report 7

Incidence of drug-related problems and adverse drug events in primary care

Version 1.1 – 2004

Translated summary
July 2004
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Version 1.1 - 2004
**Introduction**

The present evidence report on the “Incidence of drug-related problems and adverse drug events in primary care” has been prepared within the framework of “The Danish Community Pharmacy Evidence Database” of the Danish Pharmaceutical Association. The aim of the database is to ensure that the pharmacy sector has continuous access to updated knowledge of the impact of pharmacy practice.

The Danish Community Pharmacy Evidence Database consists of, on the one hand, thematic summaries of studies (an evidence report) and, on the other hand, a database that offers a possibility of searching across the literature contained in all the thematic evidence reports.

This report contains professionally analysed descriptions of studies of the incidence of adverse drug events and drug-related problems as well as a description of the total documentation within the area. Seven evidence reports have been prepared within the following areas:

1. Drug distribution and prescription handling
2. Patient information on prescribed drugs
3. Follow-up on outcomes of drug therapy (Pharmaceutical Care)
4. Self-care activities
5. Health promotion and ill-health prevention
6. Promoting rational pharmacotherapy to other health professionals

This evidence report on the incidence of drug-related problems and adverse drug events in primary care differs from the preceding six reports in that it includes studies that describe the incidence of adverse drug events and drug-related problems not only identified at the pharmacy but within the entire health sector. Furthermore, the report covers descriptive studies rather than intervention studies, as is the case in the previous six reports.

The present report covers studies published in internationally acknowledged journals and relevant Danish journals from 1990 on. Furthermore, Danish and Nordic reports of studies have been included to the extent that the editors are aware of these reports.

The primary users of the Database are the Danish Pharmaceutical Association, Danish community pharmacies and Pharmakon, Danish College of Pharmacy Practice. The Database has been developed and is maintained by Pharmakon, Danish College of Pharmacy Practice. All datasheets are included in the searchable, electronic version of the Evidence Database on www.pharmakon.dk under the heading “Apotek” and via the homepage of the Danish Pharmaceutical Association.

A summarised translation of all seven evidence reports will be prepared and made available on www.pharmakon.com under the heading “College” during 2004. The present translation is the first to be made available.

Editors: Lone Betina Damsø, Birthe Søndergaard, Dorthe Tomsen.
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Introduction

This report focuses on the incidence of problems occurring in connection with drug use. It is based on a systematic literature search and reports on two kinds of results: firstly, the result of the literature search and, secondly, the incidence of drug-related problems and adverse drug events in primary care as documented in the literature.

The literature search has been delimitated to focus on those drug-related problems, and their consequences, that are seen in the contact with the healthcare system. In view of that, the results have been reported in relation to the various settings in the healthcare system. The following categories have been used: hospitals (admissions and emergency department visits), general practice, pharmacy, and nursing homes.

The present report documents the incidence of drug-related problems and their consequences in the form of adverse drug events (for instance, hospital admissions, visits to the emergency department or other health-related consequences). In so doing, the report describes one part of the problem of patient safety. While patient safety focuses on both adverse events and errors, this report only concentrates on the incidence of drug-related problems and adverse events which can be related to drugs. Studies documenting the incidence of medication errors in connection with prescribing, dispensing, handling, and monitoring, will be examined in a future report on patient safety and errors.

This report is the seventh in a series of evidence reports. Relevant studies have been entered into “The Danish Community Pharmacy Evidence Database” equally with the studies used as basis for the previous six reports. The structure of the datasheet used in the present report to summarise the studies is different from the one used in the other reports. This is due to the fact that the subject – drug-related problems – has been examined primarily in descriptive studies, not in intervention studies. Accordingly, other criteria have been used to evaluate and describe the studies.
**Defining the area**

In recent years, drug-related morbidity has received increased attention by the health systems internationally and also in Denmark. The problem has become more visible, not least due to the implementation of quality assurance in the health sector and to an increased focus on patient safety.

The objective of this paper is to report the incidence of drug-related problems and their consequences, primarily drug-related hospital admissions and other health-related consequences.

Drug-related problems and drug-related morbidity constitute a patient safety problem. Drug-related problems can result in the patient experiencing adverse events. An adverse event has been defined by the Danish Society for Quality in the Health Sector (Dansk Selskab for Kvalitet i Sundhedssektoren) as an unintentional event which is harmful to, or carries the risk of harming, the patient, as a result of the health sector’s actions or failure to act.

This report concentrates exclusively on adverse events caused by drugs (adverse drug events).

Drug-related problems relate to the process of medical care of the patient. The consequences of drug-related problems may be health injuries to the patients, i.e. adverse drug events, possibly as the final outcome of the drug-related problem. This report uses the definition of a drug-related problem as described by Hepler and Strand (1): *An undesirable event, a patient experience that involves, or is suspected to involve, drug therapy, and that actually, or potentially, interferes with the desired patient outcome.*

According to the definition used, drug-related problems are divided into 3 dimensions, all dealing with the drug use process (2):

- **Access to drug therapy:** The patient was not receiving necessary drug therapy for a valid indication.
- **Effectiveness:** That therapy was not having the intended effect within a reasonable time.
- **Safety:** That therapy was producing an undesired effect.

There are many ways of categorising drug-related problems. This evidence report uses Hepler’s categorisation (2).

Access to drug therapy (failure to receive treatment):

1. Untreated indications
   - The patient has a medical problem that requires drug therapy
   - Potential causes: a prescription drug has not been ordered; the patient cannot afford the drug, does not accept it, cannot obtain it, or uses administration devices incorrectly.

Effectiveness of drug therapy:

2. Improper drug selection
   - The patient has a drug indication, but the drug used is ineffective, or the patient has a drug interaction that diminishes therapeutic effectiveness.

3. Subtherapeutic dosage
   - The patient is being treated with too little of the correct drug to have the desired effect.
• Potential causes: The dose is insufficient for patient’s actual need, low drug bioavailability, interactions, dispensing or administration errors, non-adherence.

4. Inappropriate use by the patient
   • The correct drug has been prescribed, but the patient does not implement, or only partially implements, the therapy for technical, physical, psychological, sociological or economic reasons
   • This category has traditionally been used in Denmark and has been maintained in the present report, as it is often difficult to establish, on the basis of available data, if non-compliance is caused by subtherapeutic dosage or overdosage.

Safety:

5. Overdosage
   • The patient is being treated with too much of the correct drug resulting in a risk of toxicity, adverse drug reactions and adverse effects.

6. Adverse drug reactions
   • The patient is having an adverse drug reaction or adverse effect to the correct drug.

7. Drug interactions
   • The patient is taking a drug which is interacting with other drugs or foods.

8. Drug use without indication
   • The patient is taking a drug for no medically valid indication.

Safety-related problems of the drug therapy may be caused by, eg: prescription errors, low drug bioavailability, dispensing or administration errors, financial problems, practical problems, lack of knowledge or non-adherence.

The link between drug-related problems and adverse events is illustrated in figure 1.
As mentioned above, there is a number of systems that classify drug-related problems; they have been developed to serve different purposes. Some of the systems tie together drug-related problems, the causes of these problems, and the practicable interventions necessary to solve the problems (cf. figure 1). This has been done to facilitate working with the classification system in practice. Some of these systems are PI-Doc, PAS and the PCNE Classification System. The various classification systems are described in more detail in the original report, Appendix 1: Terms and definitions.

In Denmark as well as in Norway and Sweden, use has been made of a classification system developed by Tommy Westerlund (3). This classification consists of the following categories:

1. Uncertainty about/lack of knowledge of the aim/function of a drug
2. Underuse of medication
3. Overuse of medication
4. Other dosage problem
5. Drug duplication
6. Drug-drug interaction
7. Therapy failure
8. Side effect
9. Difficulty swallowing tablet/capsule
10. Difficulty opening container
11. Other practical problem
12. Language deficiency/understanding disability
13. Prescription error

As the list shows, this classification holds examples of both drug-related problems (eg, underuse of medication) and the causes of these problems (eg, difficulty opening the container or swallowing the tablet/capsule).
The studies used as basis for this evidence report are primarily descriptive and report the incidence of drug-related problems and adverse drug events in primary care as a result of drug-related problems. Moreover, the report documents which patient groups at risk, which high-risk drugs and which other risk factors are of significance to the incidence of drug-related problems and adverse drug events in primary care.

Studies on medication errors in connection with prescription, dispensing, drug administration, drug handling and monitoring will be examined in a future report on patient safety and errors.

The report is divided into five subject areas:
- Incidence of drug-related hospital admissions
- Incidence of drug-related visits to the emergency department
- Incidence of adverse drug events and drug-related problems in general practice
- Incidence of adverse drug events and drug-related problems in nursing homes
- Incidence of drug-related problems identified at the pharmacy.

**Geography and setting**

The report comprises Danish studies that describe the incidence of adverse drug events and drug-related problems identified in hospitals (drug-related hospital admissions), in the primary care sector and at the pharmacy. Drug-related problems cover quality problems of drug therapies as well as patient-perceived problems.

The report includes European studies that describe the incidence of adverse drug events and quality problems of drug therapies. Review articles have been included from the remaining English-speaking world.

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Types of articles and study design
The studies used as basis for this evidence report are primarily descriptive. The following types of articles have been included:

- Meta analyses
- Review articles
- Original articles
- Reports (from Denmark and the Nordic countries).

The studies have been divided into prospective and retrospective studies, as the selected design and the applied data sources have an influence on the incidence of adverse drug events and drug-related problems in the studies. Prospective studies generally show a higher incidence.

References

Results of the literature search

Literature search
The literature search was carried out in April-May 2003. It covered the International Pharmaceutical Abstract (IPA) and Medline from 1990 until May 2003. The search strategy is attached as an appendix to the original report.

731 abstracts have been examined and assessed. Duplicates may occur. Based on their abstracts, 97 articles have been selected for review and assessment. This report covers 35 studies published in articles and reports (a total of 37 datasheets).

Geographic spreading
The evidence report on incidence of drug-related problems and adverse drug events in primary care covers 35 studies, 24 of them European.

Denmark: 12 studies
United Kingdom: 5 studies
Norway, Sweden and France: 2 studies each (6 in total)
Germany and Italy: 1 study from each country (2 in total)
USA: 10 studies.

Types of articles and subjects

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<td>Hospital admissions due to adverse drug reactions</td>
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<td>Adverse drug events</td>
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Studies which have been included in meta analyses and review articles have, for the most part, not been described as original papers, with the exception of a few of the Danish studies on drug-related hospital admissions and one Italian study. As the studies in meta analyses and original papers respectively do not constitute an overlap, the results of both categories of studies have been reported on in the overall conclusion.
Twenty studies have been carried out in hospitals. Three studies deal with drug-related visits to the emergency department. Four studies have been carried out in general practice. Five studies have been carried out in nursing homes. Finally, four studies have been carried out at the pharmacy.

**Main results in figures**

Below is the editors’ summary of the – primarily – quantitative results emerging from evaluating all the studies. They are discussed in detail in subsequent chapters of the report.

### Incidence of drug-related hospital admissions

- The meta analyses show an incidence of drug-related hospital admissions of 6-14 %
- The incidence of drug-related hospital admissions found in original articles is 4-10 %
- The meta analyses show an incidence of hospital admissions purely due to adverse drug reactions of 3-5 %
- The incidence found in original articles of hospital admissions due to adverse drug reactions is 2.5-8.0 %
- Approximately 2 % of hospital admissions are fatal
- Towards 80 % of hospital admissions are severe
- Approximately 60 % of hospital admissions are preventable, depending on disease
- Adverse drug reactions are the cause of 23-52 % of drug-related hospital admissions
- Non-adherence is the cause of 2-11 % of drug-related admissions
- Therapy failure is the cause of 2.5-4.5 % of drug-related admissions
- Cardiovascular drugs (in particular diuretics), antibiotics, pain-relievers and central nervous system (CNS) drugs are high-risk drugs with regard to drug-related hospital admissions
- The risk of drug-related hospital admissions increases with high age and an increased number of drugs. The association to gender is uncertain
- The duration of drug-related hospital admissions exceeds normal
- The costs of drug-related hospital admissions exceed normal.

### Incidence of drug-related visits to the emergency department

- Studies including a high number of patients show an incidence of drug-related visits to the emergency department of 0.05-0.6 %
- Studies including a limited number of patients show an incidence of 10-22 %
- Other studies show an incidence of 3-5 %
- 15-25 % of patients are subsequently admitted to hospital
- 30-64 % of visits are due to adverse drug reactions and adverse effects
- 28-58 % of visits are due to non-adherence
- Approximately 30 % of visits are due to therapy failure
- Cardiovascular drugs, pain-relievers, antibiotics, CNS drugs and hormones are high-risk drugs with regard to drug-related visits to the emergency department
- There is no evidence of an association between age and risk
- There is evidence that women are at increased risk.
Incidence of adverse drug events and drug-related problems in general practice

- The area has not been examined sufficiently
- The risk of falling is related to the use of CNS drugs, antidepressants, pain-relievers and cardiovascular drugs, and high age
- 24.5% of patients who refilled their prescriptions had an adverse drug event
- 3 studies of medication review in general practice show an incidence of drug-related problems in 43-44% of patients and with 56% of the drugs.

Incidence of adverse drug events and drug-related problems in nursing homes

- None of the evaluated studies assess the incidence of adverse drug events
- It is documented that nursing home residents experience many drug-related problems; most frequent are: inappropriate choice of drug, overdosage, interactions, and risk of adverse drug reactions and adverse effects
- High-risk drugs with regard to adverse drug events/drug-related problems are antidepressants, sedatives/hypnotics and antibiotics
- The risk of adverse drug events increases with the number of drugs.

Incidence of drug-related problems identified at the pharmacy

- There is evidence that pharmacy staff can identify drug-related problems among users of prescription and OTC medicines
- The incidence of drug-related problems is high. During campaigns, problems have been identified in the case of 30-40% of patients. In Pharmaceutical Care programmes, problems have been identified in 75-100% of patients
- The most frequently identified problems are: inappropriate drug use by the patient, adverse drug reactions and adverse effects, and lack of knowledge of disease and therapy
- In an international perspective, it has been documented that pharmacies intervene in 1-4% of all prescriptions
- In Denmark, it has been documented that the pharmacy intervenes in 0.5% of all new prescriptions, i.e. 200,000 prescriptions annually.

Based on international data, some of the main results have been translated into Danish circumstances and figures.

Translation into Danish circumstances and figures

- 68,000 – 158,000 drug-related hospital admissions
- 34,000 – 56,000 hospital admissions due to adverse drug reactions
- 1,400 – 3,200 of drug-related hospital admissions are fatal
- 54,000 – 126,000 of drug-related admissions are severe
- 39,000 – 120,000 drug-related hospital admissions are preventable
- 30,000 – 50,000 drug-related visits to the emergency department
- 4,500 – 12,500 patients are subsequently admitted to hospitals.
# Table of datasheets

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<thead>
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<th>Datasheet</th>
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<tr>
<td>Cannon J, Hughes CM. An assessment of the incidence and factors leading to drug-related hospital admissions in the elderly. EHP 1997;3:14-18 (Northern Ireland).</td>
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<td>Cunningham G, Dodd TRP, Grant DJ, McMurdo MET, Richards RME. Drug-related problems in elderly patients admitted to Tayside hospitals, methods for prevention and reassessment. Age and Aging 1997;26:375-382 (Scotland).</td>
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Winther L, Sørensen EW. Implementering af farmaceutisk omsorg i skranken på Brønshøj Apotek. Del III: Så langt nåede Brønshøj Apotek med registreringen af lægemiddelrelaterede problemer (Implementation of pharmaceutical care at the counter at Broenshoj Pharmacy. Part III: This is how far Broenshoj Pharmacy made it with registration of drug-related problems). Pharmakon and the Danish University of Pharmaceutical Sciences, May 1999 (Denmark).