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Medical negligence in drug associated deaths

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ABSTRACT

According to epidemiological studies adverse drug events are one of the most frequently encountered complications during medical treatment, a leading cause of hospitalisation and frequent cause of death. However, medical malpractice claims due to medication errors seem to be relatively rare. Based on a retrospective multicentre study on medical malpractice cases with lethal outcome ($n = 4450$), drug related cases ($n = 575$) were further evaluated. In 50% of cases a causal connection between drug therapy and death could be ruled out already after autopsy. In 232 cases a causal connection between drug therapy and death could be approved (drug allergies, relative overdose, wrong application, mix-up of drugs and sepsis after injection abscess). However, within the legal context only in 70 cases a medication error was approved which was in 42 cases causal for death, in 28 not. Administration of contraindicated drugs, incorrect application and relative overdose in renal insufficiency are the prevalent mistakes. Concerning the frequency of ADE in epidemiological studies medication errors are underreported in all data sources on medical malpractice; this seems to be due to the fact that even doctors and attending physicians rarely recognize an ADE; furthermore approving the connection between drug effect and death is extremely difficult for the expert witness.

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1. Introduction

According to the WHO adverse drug reactions (ADR) are defined as a noxious and unintended response to a drug occurring at a conventional dose and used for disease in prophylaxis, diagnosis, therapy or for modification of physiological functions [17]. Adverse drug events (ADE) are defined as adverse drug reactions and/or events caused by medication errors. ADE also comprise cases of medical malpractice. Causes of adverse drug reactions and events may be related to the patient, to the drug, to ambient factors and to the doctor (Fig. 1). According to older studies in 1000 patients 20–200 adverse drug reactions and 2–20 lethal outcomes have to be expected (Table 1) [19]. Based on a study on the incidence of lethal adverse drug reactions in hospitalised patients in the United States 106,000 lethal ADR per year are expected [27]. Data on the incidence of ADR are mainly available for hospitalised patients [1–6,8–12,15–19,23–28,33,36,37,38,39]. Due to the study design and the evaluation of the outcome of the incidence varies considerably between different studies. A Norwegian prospective study comprised a total of 13,992 patients who were treated in internal medicine [15,17]. Altogether 732 patients died and 133 suffered adverse drug reactions which were testified in 64 cases as direct

and in 69 cases as indirect cause of death. The incidence of lethal ADR was calculated to be 0.95%. Of the 133 lethal ADR 66 (49.6%) were classified as preventable. In 56 cases the patients presented a drug overdose; 43 patients were already hospitalised with an overdose [15,17]. If the data of the Scandinavian study were transferred to Germany taking into account 6 million hospitalisations in internal medicine per year, 57,000 lethal cases of ADR would be expected [37]. Applying the proportions of preventable ADR of the Scandinavian study to Germany, 28,000 fatal outcomes would be classified as preventable [37].

According to Pirmohamed et al. [33] the prevalence of hospital admissions due to ADR is about 6.5% (1225 of 18,820 patients) with a lethality of 0.15% or 2.3% related to the ADR-cases.

A few years ago we published the data on medical malpractice claims due to medication errors of the Institutes of forensic medicine in Cologne and Essen [31]. This study only comprised 19 cases. Obviously the data on the incidence of ADR are not mirrored in the files of the Institutes of forensic medicine or other malpractice registers concerning medical malpractice claims [7,14,20,29–32,35,40]. This is in so far astonishing as there are a lot of legal duties of physicians regarding drug therapy [21,22,32].

Meanwhile we have carried out a comprehensive study on medical malpractice claims regarding cases with lethal outcome and subsequent postmortem examination in German Institutes of forensic medicine [34,42]. The files of this study have been checked for medication errors.

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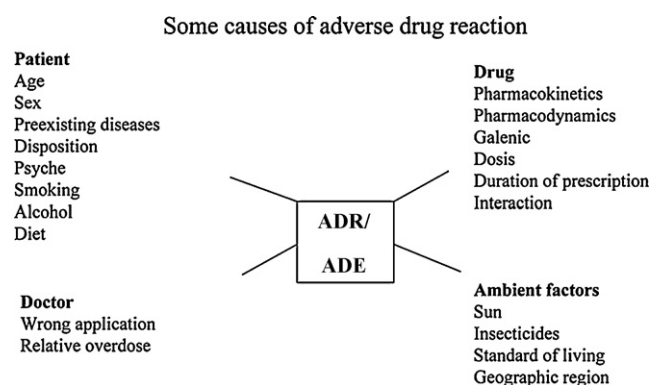


Fig. 1. Some causes of adverse drug reactions.

Table 1

Averse drug reactions according to 12 statistics (according to Gross).

In practice: (estimation)	2–5% of patients
Life-threatening	0.2% of patients
Hospitalisation due to adverse drug reaction	0.5–5.9% of hospitalisations
During hospitalisation: adverse drug reaction (international)	6.4–22.5% of hospitalisations
During hospitalisation: lethal outcome (international)	0.2–2.3%

Conclusion: in 1000 patients 20–200 adverse drug reactions and 2–20 lethal outcomes have to be expected.

2. Materials and methods

A standardized retrospective analysis on medical malpractice claims in lethal cases was carried out for the German Ministry of Health [34,42]. The multicentre analysis was based on the data of 17 German Institutes of forensic medicine and covered the time period from 1990 to 2000. Altogether 101,358 autopsy reports were checked and 4450 autopsies were due to medical malpractice (4.4%). The data were made completely anonymous. In 2860 cases only the autopsy reports, in 1587 cases autopsy reports and further comprehensive written expert evidence were available. Types of medical malpractice were classified as follows:

1. negligence
2. complications at/and or after surgery
3. wrong treatment
4. mistakes in care
5. medication errors.

For the present study cases with a possible connection between drug therapy and complications leading to death were further evaluated. Included were only cases with drug therapy irrespective of the mode and site of application, also cases with a parenteral invasive application. The cases were analysed regarding the following variables: medical discipline, kind of drug, pre-existing risks, rate of cases of approved medical malpractice. In all cases the autopsy was ordered by the public prosecutor and the expert evidence had to follow the strict regulations in penal law. The following questions had to be answered: had there been a break of duty of care? Was the mistake or error followed by a damage leading to death? Could the causal connection be proved without reasonable doubts?

3. Results

In 575 (12.5%) of 4450 cases medical malpractice claims were due to medication errors. The proportion of claims due to medication errors was quite constant over the study period although the number of cases increased (Fig. 2). In nearly 50% the criminal proceedings were against hospital doctors ($n = 273$) followed by doctors in private practice ($n = 198$, 35.5%) (Fig. 3). Emergency service doctors were concerned in 26 (4.7%) cases, nursing staff in 23 (4.1%) cases. Regarding the medical specialties conservative disciplines were more frequently concerned with medical malpractice claims (Fig. 4). Internal medicine was concerned in 107 (19.2%) of 557 cases followed by general practitioners ($n = 76$, 13.6%). The patients were mainly elderly men ($n = 262$) and women ($n = 295$).

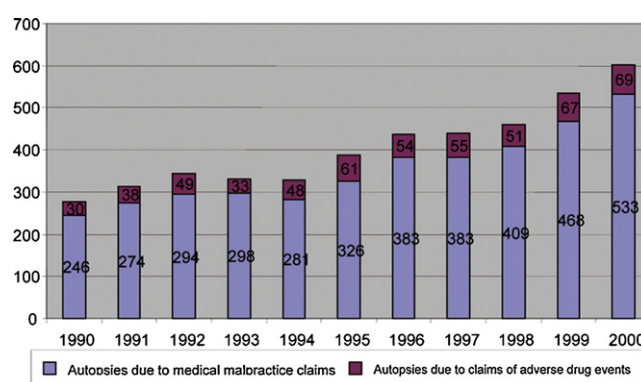


Fig. 2. Claims of medical malpractice due to medication errors. Proportion of cases on all autopsies due to medical malpractice.

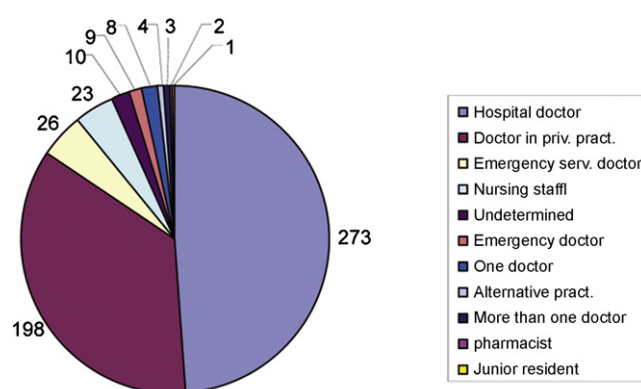


Fig. 3. Occupational groups concerned by accusation of medical malpractice.

Medication errors were classified as follows: wrong drug, wrong dose, incorrect application, incorrect discontinuation of drug, incorrect prescription, adverse drug reaction and claim not specified. The claims wrong drug ($n = 107$, 19.2%), wrong dose ($n = 131$, 23.5%) and adverse drug reactions ($n = 109$, 19.6%) were encountered frequently while the claim of incorrect discontinuation of drug ($n = 72$, 12.9%) and wrong application ($n = 47$, 8.4%) were seen less frequently (Fig. 5). After the medico-legal autopsy already in 50% of cases (284 of 557) the causal connection between drug therapy and death could be ruled out since morphological clear causes of death were evident without causal connection with drug therapy (Fig. 6). These 284 cases were not analysed further since medical malpractice claims due to wrong drug therapy could be ruled out.

3.1. Cases with causal connection between drug therapy and death

In 232 cases there was a causal connection between drug therapy and death, however, in 45 cases due to severe underlying disease there was no sufficient evidence that death was due to drug therapy alone (Fig. 7). In 102 of these 232 cases death was due to known side-effects or allergic reactions with anaphylactic shock. In 6 cases death was due to sepsis after injection abscesses. In 57 cases death was due to over or false dose and in 21 cases due to wrong application of the drug.

3.1.1. Death due to side-effects and allergic reactions

These 102 cases make up only a small part of all cases (18.3% of cases with malpractice claims due to medication errors or 2.3% of all 4450 cases of medical malpractice). Leading drug groups were contrast media (19×), anti-coagulants (18×), marcumar (4×), heparine (7×), lyse therapy (7×) followed by antibiotics and non-

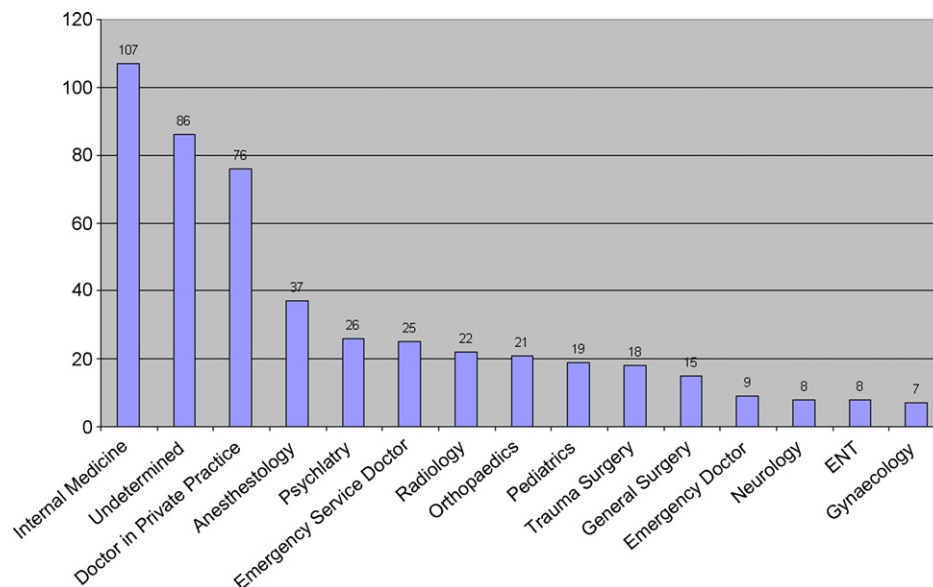


Fig. 4. Medical malpractice claims, classification according to medical disciplines.

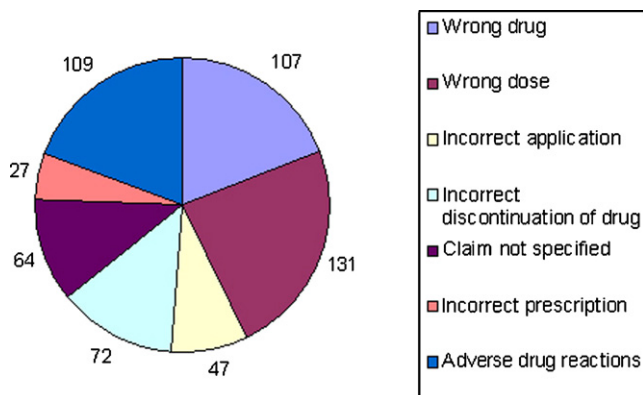


Fig. 5. Classification of medical malpractice claims in drug associated deaths.

steroidal anti-rheumatics (NSAR) with 9 cases each. Concerning the last group only 2 drugs were involved: 5× diclophenac and 4× metamizol. Local anaesthetics were seen in 6 cases, chemotherapeutics in 5 cases (3× methotrexate), opioids in 4 cases. Cases with death due to side-effects and allergies were mostly seen in

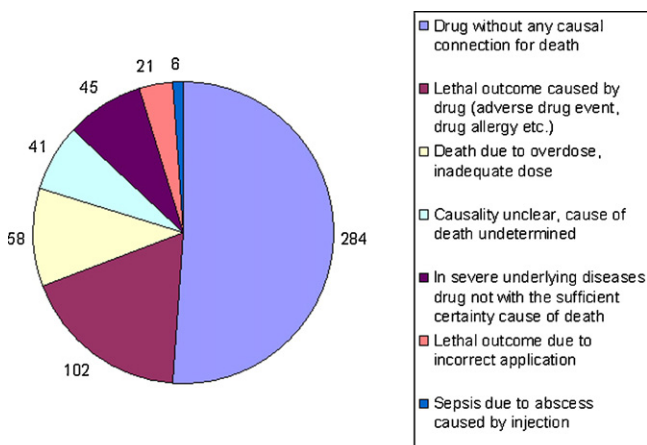


Fig. 6. Medical malpractice in drug associated deaths – autopsy results (n = 557).

hospitals (n = 65), in 32 cases in the ambulant sector. Known side-effects were mainly seen in elderly patients, two-thirds of patients were 50 years and older with several pre-existing diseases.

3.1.2. Cases with a lethal overdose or wrong dose

Among 57 cases with a lethal over or wrong dose opioids were seen in 14 cases. In 10 cases an intoxication with benzodiazepines in combination with other drugs, e.g. methadone, was cause of death. The following further drugs were concerned: psychopharmacologic medication (7×), non-steroidal anti-rheumatics (6×), cardiac glycosides (4×), chemotherapeutics (methotrexate) (4×), insuline (2×), sodium (2×). Most cases were seen in the ambulant sector of health care (33×). Of special interest was the non-controlled disposal of methadone and benzodiazepines to drug addicts. 21 cases were seen in hospitals. In all cases of relative overdose of methotrexate pre-existing renal diseases were not considered properly.

3.1.3. Cases with wrong application or mix-up of drugs

Among 21 cases with application of wrong drugs 8 were due to potassium infusions. Mostly potassium and sodium chloride were mixed up. In 3 cases an anti-neoplastic drug was administered intrathecal (2× vincristine and 1× farmorubicine). In 3 cases the nursing staff applied injection machines incorrectly. In 2 cases local anaesthetics were applied before chiropractic treatment resulting in severe injuries of the cervical medulla. Further cases were due to intrathecal administration of methotrexate and other wrong applications (intravenous injection of a local anaesthetic).

3.1.4. Sepsis after injection abscess

From 6 cases of a lethal sepsis after injection abscess 4 cases were due to intramuscular injection, 2 cases due to subcutaneous injection.

3.1.5. Severe pre-existing diseases as contributory factor for death

In 45 cases as a result of autopsy and further investigations medication errors were not the single cause of death due to severe pre-existing underlying diseases (Table 2). Leading pre-existing diseases were cardiovascular diseases in 23 cases. In this group 24 women and 21 men were seen. Concerning the age the female patients were either children or older people, the male patients were mainly aged between 50 and 59 (Fig. 8).

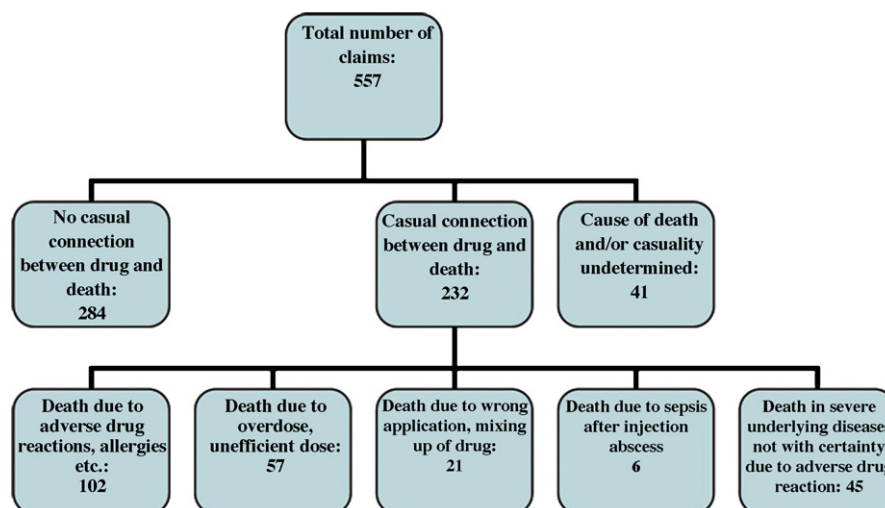


Fig. 7. Flow chart regarding all cases of medical malpractice claims in drug associated deaths.

Table 2

Underlying diseases in cases in which drugs were not the cause of death with the sufficient certainty.

Underlying disease	Number of cases
Coronary heart disease, heart insufficiency	15
Apoplexy, arterial hypertension	5
Tumor/carcinoma	3
Infantile brain damage	3
Pulmonary thromboembolism	2
Peritonitis	2
Generalised atherosclerosis	2
Asthma bronchiale	2
Vitamine K deficiency	1
Mitochondriopathia	1
Myocarditis	1
Pneumonia	1
Epilepsy	1
Alcoholism	1
HIV infection	1
Trisomia 18	1
Cholangitis	1
Generalised vasculitis	1
Enteritis	1

Table 3

Medical malpractice and drug therapy – types of mistakes.

	Causality +	Causality –
Administration of a contraindicated drug (disregarding drug allergy)	18	11
Incorrect application/mixing-up of drugs	11	4
Wrong dose (overdose)	7	10
Administration contraindicated regarding further medical interventions	2	–
Right drug was not given	4	1
Only symptomatic therapy	–	2
Total	42	28

malpractice the administration of a contra-indicated drug disregarding drug allergy was the prevalent mistake (Table 3). An incorrect application of drugs was seen in 15 cases, an overdose in 17 cases. In cases of approved medical malpractice due to medication errors the following drug-categories were involved (Table 4).

4. Discussion

In the present study the number of allegations of incorrect drug therapy is rather low with 12.4% of autopsies due to medical malpractice claims and 0.55% of all autopsies. Allegations of wrong drug therapy are quite rare taking into consideration the total number of liability lawsuits and preliminary proceedings against physicians [20,29,31].

The discrepancy between epidemiological data on ADE and medical malpractice claims was already referred to several years ago and becomes also obvious from other data sources (arbitration committees, liability insurers and health insurers). Thus, the various data sources should be consolidated for further investigations.

The small number of allegations of wrong drug therapy might be due to the fact that ADE are difficult to detect not only for medical laymen but also for physicians. In a Scandinavian study physicians suspected an ADE only in 8 (6%) of 133 ADE based deaths. Thus, in 94% of cases there was no suspicion of an ADE [15]. The number of ADE relevant to criminal law is most likely much higher than currently stated.

The low frequency of allegations of wrong drug therapy is also mirrored in the current civil and penal judicature on lethal ADE which is not very extensive [21,22,32].

While an estimated number of unreported cases of medical malpractice due to ADE can be expected taking into consideration

3.2. Results of expert evidence

Regarding all 557 cases of medical malpractice due to medication errors in the majority of cases ($n = 366$, 65.7%) no malpractice could be proved. In 70 cases (12.4%) a medication error was approved which was in 42 cases causal for death, in 28 cases not. Concerning the types of mistakes in cases of approved medical

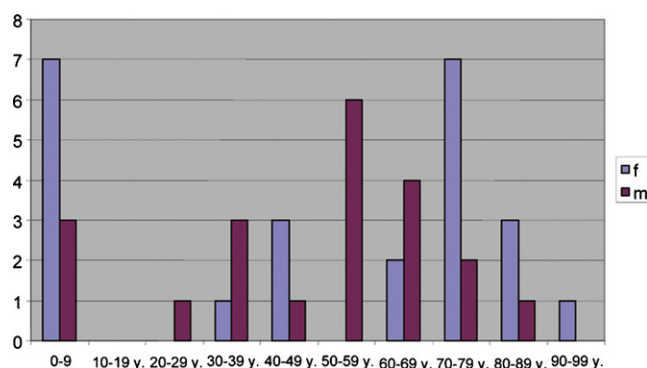


Fig. 8. Distribution of age in cases of severe underlying diseases ($n = 45$).

Table 4
Distribution of drug categories.

Drug categories	Causality confirmed	Causality negated
Chemotherapy	5	4
Corticosteroids	2	
Local anaesthetics	2	
Antiemetics	1	
Substitution therapy	5	
Antiarrhythmics	3	
Infusion therapy	6	5
Analgetics (except for opioids)	3	1
Opioids	2	1
Antiphlogistics	1	1
Contrast medium	2	1
Antiparkinson drug	1	
Evacuant	1	
Heparin	1	2
Digitalis	1	2
Antidepressives	1	
Adequate drug withdrawn	1	
Antibiotics	1	2
Appetite suppressant	1	
Beta-blocker	1	
Muscle relaxant	1	
Spasmolyticx		1
Psychotropics		1
ACE inhibitor		1
Naturopathic treatment		3
Insulin		3
Antiepileptics		1

epidemiological data in the own retrospective analysis already the autopsy revealed in half of the cases no causal connection between medication and death. Only in 232 cases (0.23%) of all autopsies performed in the 11 years investigated a connection between medication and death could be derived. Causes for ADE could be found on the part of the patient, of the drug and also on the part of the physician.

Epidemiological studies verified as prevailing drugs leading to hospitalisation aspirin, diuretics, warfarine, non-steroidal anti-rheumatics [33].

Regarding groups of drugs involved there is no clear tendency in this retrospective study. ADE in connection with infusion therapies or chemotherapies could be found quite frequently. A mix-up of potassium and sodium chloride as well as an incorrect intrathecal injection during a chemotherapeutic treatment are errors in treatment which do occur repeatedly although they could be easily avoided. Identification of such errors in treatment in the context of medico-legal evaluation of medical malpractice claims also provides a basis for prophylaxis of medication errors. Thus, a report on 2 cases of inadvertent intrathecal administration of vincristine [13] and comparable cases were recognized by the German drug commission of the federal Medical Council and recommendations to prevent false administrations were published.

In one of the previous studies psychotropics were identified as a group of drugs which is involved frequently in medical malpractice claims [31]. The incorrect simultaneous prescription of methadone and benzodiazepine can also be noticed quite frequently in the present study.

Although the number of hospital doctors who are accused of incorrect drug therapy is still prevailing, the number of doctors in private practice is almost as high. The rate of medical malpractice cases with approved causality for death is 6.2% for hospital doctors and 9.6% for doctors in private practice. This is of special importance since most epidemiological studies on ADE are focussed on hospitalised patients.

For patients with severe pre-existing diseases it becomes quite difficult to decide on the causal connection between medication and death. In 45 cases it could not be proved without doubt that

medication and/or ADE respectively alone caused death. Taking into consideration the pre-existing diseases there is an accumulation of cardiovascular diseases as concurrent cause of death.

Typical fatal ADE occur in old patients, multi-diseased patients, patients using multiple drugs already at hospital arrival and patients receiving 4 or more drugs during hospitalisation [17]. In such patients one should anticipate altered absorption of drugs, changed (often reduced) metabolism of many drugs, altered distribution, altered (often reduced) excretion and reduced homeostatic mechanisms. Furthermore an increased sensitivity to various drugs and/or drug/drug interactions and drug/disease interactions have to be taken into account. However, they are often not recognized or suspected, even not in fatal cases. When giving expert evidence in cases of medication errors the following points should be noticed [15,17,30]:

- Indication for the administered drug.
- Selection of the appropriate drug.
- Informed consent for therapeutical reasons given?
- Was the course of the disease checked, were serum drug analyses carried out?
- Was the success of the drug therapy controlled and how?
- Was the dose selected according to age, body weight, renal and hepatic function and appropriate for disease pattern to be treated? Was the clinical diagnosis correct?
- Wrong diagnosis leads of course to inappropriate drug choice.
- Was the profile of the ADE outside of the pharmacodynamic profile or within the pharmacodynamic profile (toxic reactions) (Table 5)?

Medication errors with a profile of the ADE outside of the pharmacodynamic profile are easy to clear up when a drug allergy was not taken into consideration. ADE within the pharmacodynamic profile (toxic reactions) are also easy to clear up when the dose is over the therapeutic range (overdose). In cases with doses within the therapeutic range the question of drug/drug interaction has to be checked. ADE beyond the pharmacodynamic profile (allergies) are not due to an error or negligence by the physician if the allergy was not known. However, if an allergy was known but not considered or not retrieved, or if an individually contra-indicated drug was prescribed, or if dosages were not adjusted in cases of pre-existing diseases, a resulting ADE might be judged as an error in treatment.

Furthermore the grade of causal connection between drug therapy, medication error and adverse event (questionable, possible, probable, sure) has to be addressed.

In the Norwegian study a grading of connection between drug effect and death was proposed as follows [15,17]:

The drug alone was sufficient and necessary to cause death.

The drug was sufficient, but not necessary to cause death; no other causes of death apparent.

Table 5
Profile of ADR.

Profile of ADE
Outside of the pharmacodynamic profile
Drug allergy
Pseudoallergy
"Idiosyncrasy"
Within the pharmacodynamic profile (toxic reactions)
Dose outside of (over) the therapeutic range
Overdose
Dose within the therapeutic range
Drug/drug interaction
Connection with ADE questionable, possible, probable, secured

The drug was sufficient, but not necessary to cause death. Evidence that other causes initiated the death process.

The drug was sufficient to start the death process, provided toxic drug levels were found.

Paying attention to these memo list helps to give a sound expert evidence in cases of medication errors. However, the difficulties in evaluating an association between death and drugs are also well known in clinical pharmacology: “Thus without having access to autopsy data and drug analysis data clinicians are “walking in the fog” as far as detecting fatal ADEs is concerned” [17].

In the present study 70 cases of incorrect drug therapy were classified as preventable. This corresponds to 30% of all cases with a causal connection of medication and death. According to the medico-legal expertise death could have been prevented in 42 of those cases. In cases of approved medical malpractice the main mistakes were the administration of a contraindicated drug followed by wrong application of a drug or mix-up of drugs connected with a relative overdose.

The files of the Institutes of forensic medicine on medical malpractice claims provide data on events that are significant – serious injuries – as well as data that are typically much more comprehensive than provided to most reporting systems [41]. Therefore case reports or case series e.g. on mix-up of drugs or wrong applications can contribute to increase patient safety. Contributing to an increase of patient safety is also a task of forensic medicine and this contribution can easily be achieved by analysing the own files. However, cases should also be sampled on a national or international level.

5. Conclusion

Accusations of incorrect drug therapy represent only a small part of medical malpractice claims regarding lethal cases and they have remained constant during the last years. A causal connection between death and medication therapy can only be proved in half of the cases. Taking into consideration the incidence of ADE it becomes obvious that there has to be an estimated number of unreported cases of medical malpractice cases due to ADE relevant for civil and penal prosecution. In 30% of cases the medication error is classified as preventable, in 18% death could have been prevented with correct medication. Identification of risk constellations in retrospective medico-legal evaluation of medical malpractice claims also provides a basis for prophylaxis of medical negligence by development of appropriate recommendations. ADE risk groups which were identified in clinical–epidemiological studies were confirmed in the present retrospective study. Thus, there are repeated cases of relative overdoses due to missing adjustment in patients with limited renal function. In cases of wrong application, mix-up of drugs etc. there can be observed a mixture between individual and system failure and it is one of the medico-legal tasks to identify these failures and, thus, to contribute to error prophylaxis and patient safety.

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