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Drug-Related Problems Causing Admission to a Medical Clinic

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Summary. The association between hospital admission and drug-related problems was evaluated in 285 consecutive admissions to two medical wards in a Swedish university hospital. Standardised definitions and criteria for causality were used. A drug-related problem was judged to have been the main reason for admission of 36 patients, and a strongly contributory reason for 9. These 45 patients comprised 16% of all patients, and 19% of those receiving medication prior to admission. For 19 patients the problem was considered to be failure to achieve the desired therapeutic effect. 11 of these 19 took less medication than prescribed, and an inadequate dose had been presented for the other 8 patients. In 26 patients there was an excessive or otherwise adverse effect. In 10 it was an intentional or accidental poisoning, and 16 had an adverse drug reaction. Non-compliance with the prescribed regimen caused almost half of the drug-related admissions: 11 took too little and 10 took too much of the prescribed drugs. The majority of the other problems could probably have been prevented by better application of pharmacokinetic principles to the prescribing.

Key words: drug problems, patient compliance; adverse drug reactions, interview, pharmacokinetics, inadequate therapy

Since the early 1960's there has been much concern about adverse reactions and other problems associated with increased consumption of drugs. Adverse drug reactions (ADRs) have been reported in 6 to 35% of hospitalised medical patients [1–11], and to account for 2 to 9% of all admissions to medical clinics [12–18].

Ineffective treatment due to poor patient compliance has been recognised during the past 10 years as another important pharmacotherapeutic problem. On average, only about half the patients on long-term drug treatment have been found to be compliant [19], and non-compliance has been identified as further drug-related problem leading to hospital admission [15].

Many methodological problems in assessing and evaluating patient compliance and ADRs have been pointed out [17, 19, 20, 21, 22], and a call has been made for more standardised and accurate methods. This study is an attempt to evaluate the role of different types of drug-related problems in causing hospital admissions by use of standardised definitions and cause-effect criteria.

Methods and Clinical Setting

As a part of a drug surveillance study [23, 24], consecutive patients admitted over a 3.5 month period to two (out of six) wards in the Department of Internal Medicine of a Swedish university hospital were investigated for drug-related problems. The problems considered were: patient non-compliance with prescribed drug regimen (i. e. taking more or less than prescribed), undertreatment by doctors and ADRs.

Information about previous drug treatment was obtained by interviewing the patients on the first day in the wards (rarely later). The interviews were conducted by two experienced research nurses with special training in interview technique, or by the authors. Additional information was obtained from relatives, home aids, case reports or referral notes [24].

Blood samples for drug analysis (digoxin, digitoxin, phenytoin, carbamazepine and phenobarbital) were collected prior to dose administration on the first morning in the wards, and when possible, were repeated after supervised drug intake between Days 7 and 9. The samples were analysed according to the routine of our Clinical Pharmacology labora-

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tory [24]. Samples were also taken at other times when clinically indicated. The drug therapy of the patients was surveyed during their hospital stay, and relevant information, clinical and laboratory, was recorded [23]. Apart from the blood samples for drug analysis, we did not actively interfere with the routine health care. Drug plasma levels in the potentially toxic range were immediately reported to the clinicians and other values were given on request.

Patients

In all, 291 patients were admitted during the study. Information on previous drug treatment was not obtained from six patients; 4 for clinical reasons, 1 because of language problems, and 1 patient was missed; these patients have been excluded from the calculations. The remaining 285 patients comprised 141 men and 144 women, aged 16 to 97 years (mean 59 years, SD ± 19). There was no significant difference in mean age between the men and women. The average duration of stay in the wards (12 days, including the days of admission and discharge) did not differ significantly from the average for the entire medical department (11 days). In all, 190 patients (67%) were acute admissions, 81 were elective admissions and 14 were transferred from other wards or hospitals. Cardiovascular (21%), malignant (20%) and gastrointestinal (10%) diseases were the most common principal diagnoses. Prior to admission, 46 patients were not taking any drugs, 217 patients had received 799 prescription drugs, and 52 patients were taking 65 OTC drugs as self medication [24].

Classification and Definitions

In evaluating drug problems, a broad distinction was made between symptoms resulting from excessive or adverse drug effects on the one hand, and failure to accomplish the intended purpose of the treatment on the other. An evaluation was also made of the role of patient non-compliance in causing the drug problems studied.

Table 1. Inadequate or no effect of prescribed therapy in 11 non-compliant patients

No	Sex	Age [years]	Signs and symptoms and causes	Cause-effect relation	Reason for admission
1	M	66	Hypertension, poor control during irregular intake of furosemide and alprenolol	probable	Main
2	F	74	Hypertension and heart failure aggravated after stopping furosemide treatment	probable	Main
3	M	80	Heart failure, aggravated while not taking bendroflumethiazide and spironolactone and probably not digoxin as prescribed. Plasma digoxin increased from 1.2 to 2.1 nmol/l with unchanged digoxin dosage during hospitalisation	probable	Main
4	F	76	Heart failure aggravated while taking a lower dose of furosemide than prescribed	probable	Co
5	F	73	Heart failure aggravated after not taking more than half the dose of furosemide and no digoxin for a week (p-digoxin <0.4→1.3 nmol/l)	probable	Main
6	F	86	Heart failure repeatedly aggravated by uncontrolled and irregular intake of digoxin and furosemide	definite	Main
7	F	82	Heart failure aggravated after not taking furosemide for a week	probable	Main
8	M	55	Gastritis aggravated after stopping antacid and anticholinergic treatment (clidine + chlordiazepoxide and bensilone)	probable	Co
9	M	32	Gastritis aggravated after stopping antacid and anticholinergic treatment (propantheline)	probable	Main
10	M	37	Duodenal ulcer during sporadic and irregular intake of propantheline prescribed for gastritis	probable	Co
11	M	84	Bronchial asthma aggravated after stopping a theopylline-ephedrine-guaiphenesin compound	probable	Co

Mean age 68 years

Table 2. Inadequate effect of drug treatment in eight patients without evidence of non-compliance

No	Sex	Age [years]	Signs and symptoms and causes	Cause-effect relation	Reason for admission
12	M	41	Epileptic seizures after inapropriate reduction of phenytoin dose subsequent to intoxication (plasma phenytoin decreased from 210 to 29 μmol/l)	probable	Main
13	M	39	Epileptic seizures after change of phenytoin brand (due to shortage) causing loss of therapy for one day (p-phenytoin 35 μmol/l on admission)	probable	Main
14	M	39	Epileptic seizures on the fourth day after changing primidone and phenobarbital to carbamazepine	probable	Main
15	M	55	Epileptic seizures at subtherapeutic plasma concentrations (<4 μmol/l) of phenytoin (brand with low bioavailability). Patient also had low plasma concentration of phenobarbital (8 μg/ml)	probable	Main
16	M	72	Heart failure aggravated 14 days after a change from digoxin to digitoxin	probable	Main
17	F	70	Heart failure on a digoxin dosage giving plasma concentration of 0.8 nmol/l with a low dose of hydrochlorthiazide (12.5 mg/d)	probable	Co
18	M	61	Hypertension and tachycardia (atrial fibrillation) poor control probably due to undertreatment with clonidine and digoxin (p-digoxin 0.8 nmol/l)	probable	Main
19	M	48	Hypertension, insufficient effect of alprenolol and hydrochlorthiazide	probable	Co

Mean age 53 years

ADRs were defined as: "any response that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy, excluding a failure to accomplish the intended purpose" [20]. This definition excludes intentional and accidental poisonings as ADRs, and they are presented as separate groups.

Failure to accomplish the intended purpose of a drug treatment may be due to errors in diagnosis, choice of drug, suboptimal dosage and/or failure to receive the prescribed regimen. We did not include admissions due to errors in diagnosis or in choice of drug (e. g. an antibiotic to which the bacteria were resistant), nor patients who were admitted before the full effect of drug therapy for a recently discovered disease could have been expected.

We used the following definition of patient compliance: "the extent to which the patients behaviour (in terms of taking medication, following diets or executing other life-style changes) coincides with the clinical prescription" [19]. This definition, agreed upon in a 1974 symposium on patient compliance, includes over- as well as under-consumption of drugs.

Evaluation of the cause-effect relationship between signs and symptoms in the patients and their drug treatment were based on criteria suggested for ADRs [20], but were generalised to cover a lack of drug effect:

1) A reasonable temporal sequence from the commencement or cessation of the drug treatment.
2) Drug levels established in body fluids or tissues compatible with the signs or symptoms.
3) A known response pattern.
4) The signs or symptoms were improved by dose adjustment, stopping or reinstitution of the drug therapy.
5) The signs and symptoms could not reasonably be explained by the known characteristics of the patient's clinical condition.
6) The signs and symptoms could not reasonably be explained by the effects of other drugs.
7) The signs and symptoms reappeared on repeated exposure to the previous drug regimen.

Depending on the criteria met, the cause-effect relationship was classified as follows [20].

definite:	1 or 2 + 3 + 4 + 5 + 6 + 7
probable:	1 or 2 + 3 + 4 + 5 + 6
possible:	1 or 2 + 3 + 4
conditional:	1 or 2 + 4 + 5 + 6
doubtful:	all others

Table 3A. Intentional poisoning in three patients

No	Sex	Age [years]	Signs and symptoms and suspected drugs	Cause-effect relation	Reason for admission
20	F	23	Coma, attempted suicide with nitrazepam, diazepam and methaqualone	probable	Main
21	M	30	Coma, attempted suicide with promethazine and diazepam	probable	Main
22	F	43	Coma, attempted suicide with nitrazepam, thioridazine and levomepromazine	probable	Main

Table 3B. Accidental poisoning in seven patients

No	Sex	Age [years]	Signs and symptoms and suspected drugs	Cause-effect relation	Reason for admission
23	F	80	Coma after intake of repeated doses of an analgesic/barbiturate compound (6–15 tablets) because of back pain	probable	Main
24	M	51	Stupor after intake of repeated doses of carbamazepine (2.8 g, max conc 96 μmol/l)[a] for alcoholic abstinence	probable	Main
25	M	26	Hypoglycemic coma after insulin and alcohol intake without food	probable	Main
26	M	37	Hypoglycemia after intake of chlorpropamid and alcohol without food	probable	Main
27	F	82	Hypoglycemia after intake of insulin without food. Also non-compliant with digoxin with an increase of p-digoxin from 0.4 to 1.4 nmol/l during hospitalisation	probable	Main
28	F	69	Gastritis acutely aggravated after intake of repeated doses of an analgesic compound (containing aspirin) for back pain. Stopped taking prescribed antacids during the same period	probable	Main
29	M	28	Gastritis aggravated during a week with high aspirin intake (~ 3 gm/day) because of headache	probable	Co

Mean age: A 32 years
B 53 years

[a] Toxic levels = >40 μmol/l

Only cases with a definite or probable cause-effect relationship were included [20]. In this study we considered it less important to identify a specific drug as causing the problem than when evaluating only ADRs. Therefore, cases have been included as "probable" if the combined action of two or more drugs fulfilled our criteria.

We regarded the drug problem as the *main reason* for admission if all signs and symptoms causing the hospitalisation could be attributed to the drug problem. If the patient had coexisting problems that were not minor (cf patient No. 29), or if the symptoms only decreased after correcting the drug problem, we regarded it as a *co-reason* (e. g. patient No. 34, who was still mildly dizzy after drug withdrawal).

The assessment of patient compliance was usually based on statements by the patients during the interview, or by their relatives, home aids etc. [24]. When possible, changes in drug levels after supervised drug intake were considered. The cause-effect relationship between the medication behaviour of the patients and the signs and symptoms leading to hospitalisation were also evaluated according to the above criteria.

Mean values ± S.D. are given. Differences between means were tested with Student's *t*-test and differences in distributions by the chi-squared or Fisher's exact tests.

Results

In all, 45 of the 285 admissions (16%) were judged to have been associated with drug-related problems (main reason in 36 and co-reason in 9); an inadequate drug effect, resulting in failure to accomplish the intended purpose, was identified in 19 of them

(Tables 1, 2). Accidental or intentional poisoning was responsible for 10 admissions (Table 3), and ADRs for 16 (Table 4). Non-compliance with the prescribed regimen was judged, therefore, to have caused the admission of 21 of the 45 patients (Table 5). Among the patients prescribed drugs (n = 217), significantly more men than women (p = 0.026) were admitted because of insufficient drug effect (without evidence of non-compliance; Table 2).

By contrast, ADRs seemed to have caused admission more often for women ($p = 0.043$) among those taking prescription or OTC drug ($n = 234$). Significantly more ($p < 0.05$) patients for whom 4 or more drugs had been prescribed (11.1%) were admitted because of ADRs than of those receiving up to three drugs (3.6%).

Except for the three patients with a suicide attempt (Table 3 A), the mean ages in the different groups (Tables 1–4) did not differ significantly from the rest of the patients. The average weight of women with (60 ± 10 kg) and without (61 ± 12 kg) ADRs did not differ significantly. The average weight of the seven undertreated men (60 ± 24 kg) did not differ significantly from that of the other men (72 ± 14 kg). All of the patients with ADRs had normal serum creatinine (<120 nmol/l).

Discussion

In this study a drug-related problem was a common reason for admission. Most prior studies have focused on the role of ADRs in hospital admissions [12–18]. We found an inadequate therapeutic effect to be equally important. Moreover, when overdosage was included, non-compliance with the prescribed regimen caused almost half of the drug-related admissions (Table 5). Insufficient drug intake identified by interview was the cause of an even larger percentage of hospital admissions (10.5%) in another study [15]. Because patients often underreport but seldom exaggerate non-compliance [19, 25], this problem may have been underestimated. Reported non-compliance was confirmed by monitoring drug concentrations in certain cases (e. g. Nos. 3, 5, 27). Suspected but unreported non-compliance was similarly excluded in others (Nos. 15, 17, 18). One of these patients (No. 15) was initially suspected of not having taken phenytoin as prescribed, because he had an unmeasurably low serum concentration, but this proved instead to be a bioavailability problem [26, 27]. In all, eight cases of inadequate drug effect without evidence of non-compliance were identified (Table 2). After correcting the dosage (Cases Nos. 12, 15, 17, 18, 19), or awaiting the establishment of new steady state plasma levels of the drugs (Nos. 13, 14, 16), the patients were again well controlled (Case No. 15 was given a phenytoin brand with better bioavailability). Thus, many of these problems could probably have been prevented by closer monitoring of drug levels.

Intentional or accidental poisoning has been reported to cause 1–4% of hospital admissions [12, 14, 15, 16]. Neither these reports nor our study can reveal the true impact of intentional poisoning, because they were restricted to medical patients. It may be questioned whether the hypoglycaemic reactions (Table 2; Nos. 25–27) or the patients with gastritis (Nos. 28, 29) should have been classified as ADRs rather than poisonings. We consider them as poisonings, because we judged the medication behaviour of the patients to have been the ultimate cause of the adverse events. However, much of the blame falls on the health care system, since the responsibility for provision of adequate information to patients about drug effects rests with the prescribing physicians and the dispensing pharmacists.

The proportion of patients admitted because of ADRs (5.6%) was of the same order as that reported in other countries [12–15, 18], but was somewhat lower than that in another Swedish study, which included cases labelled as "possible ADRs" [16].

Polypharmacy, high age and female sex have often been identified as "risk factors" for developing ADRs [2, 9, 12, 13, 16, 18, 28]. However, these factors often coincide [9, 12, 24], and as the majority of reported ADRs seem to be dose-dependent, they are probably often primarily caused by failure to individualize therapy.

In this study 3 elderly patients (Nos. 35, 36, 40) developed dose-dependent reactions after receiving relatively high doses of drugs which are excreted by the kidney in active form (chlorthalidone, hydrochlorothiazide and amantadine). This illustrates the importance of recognising that elderly patients have a decreased capacity to excrete such drugs, even at a "normal" serum creatinine value [29]. In fact, most of the ADRs were due to the primary pharmacological effects of the drugs, and all but three (Nos. 39, 41, 42) could probably have been prevented by more appropriate dosage.

The types of ADRs and the drugs identified vary in different studies. This can be explained by differences between the patient series, as well as variation in the prescribing habits of the physicians [18, 24].

The strictness of the cause-effect criteria used is also important [17, 20–22]. Six patients were hospitalized because of suspected digoxin intoxication, but in none could this be confirmed, neither clini-

Table 4. Adverse drug reactions in 16 patients

No	Sex	Age [years]	Signs and symptoms and suspected drugs	Cause-effect relation	Reason for admission
30	F	75	Acute gastrointestinal bleeding during treatment with prednisolone, proxyphylline and warfarin (protrombin value <5[a])	probable	Main
31	F	46	Anemia after repeated large menstrual bleedings and hematuria during dicoumarol treatment (protrombin value <5[a]). Concurrent treatment with chloralhydrate may have potentiated the dicoumarol effect	probable	Main
32	M	39	Orthostatic hypotension with dizziness after an abrupt change from placebo to full dose of alprenolol (600 mg/day)	probable	Co
33	F	59	Orthostatic hypotension during treatment with bendroflumethiazid after a dose increase of alprenolol from 200 to 400 mg/day (Bp[b] 125/90 supine, 100/80 standing up)	probable	Main
34	F	54	Relative hypotension with dizziness and transitory cerebral ischaemia after an increase from 40 to 240 mg of propranolol per day in a patient with mild carotid stenosis (Bp 130/85 supine, 115/80 standing up)	probable	Co
35	F	92	Hypotension on chlorthalidone 50 mg and methyldopa 750 mg/day (Bp 110/80 supine)	probable	Main
36	F	83	Hypotension on hydrochlorothiazide 75 mg/day (Bp 140/95 supine, 110/80 standing up)	probable	Main
37	F	76	Palpitations and tachycardia (pulse rate 130/min, atrial fibrillation) after a dose increase of hydralazine from 50 to 75 mg/day. Hypokalemia (3.2 mmol/l) from bendroflumethiazide. Plasma digoxin concentration 0.8 nmol/l	probable	Main
38	F	96	Shock 20 min after spinal anaesthesia with a high dose of tetracaine (18 mg) for fracture of femoral neck	probable	Main
39	F	42	Hypovolemic shock caused by excessive bowel emptying after laxative suppository (bisacodyl) in a dehydrated mentally retarded patient	probable	Main
40	M	81	Orthostatic hypotension and episodic confusion during treatment with nortriptyline and furosemide after a dose increase of amantadine from 200 to 300 mg/day (Bp 170/60 supine, 120/60 standing up)	probable	Main
41	F	20	Deep venous thrombosis of a leg during treatment with oral contraceptive (lynestrol 2.5 mg + ethinyloestradiol 0.05 mg) in a smoking but healthy woman without trauma	probable	Main
42	F	69	Cholestatic jaundice after 3 weeks treatment with increasing doses of chlorpromazine (up to 400 mg/day)	probable	Main
43	F	78	Nausea, vomiting, fatigue and diplopia since taking a prescription of an aspirin-dextropropoxyphene compound for back-pain	probable	Main
44	M	82	Muscular hypotonia with attacks of falling and slight intoxication after two weeks treatment with diazepam 10 mg/day	probable	Main
45	F	62	Repeated hypercalcaemia and renal insufficiency during treatment with calciferol because of hypocalcaemia after thyroidectomy	definite	Main

13 women and 3 men with a mean age of 66 years

[a] Therapeutic range (10–20), Simplastin A

[b] Bp = blood pressure in mmHg

Table 5. Relation between drug effect and patient medication behaviour in 45 patients with drug-related hospital admissions (n = 285)

Drug effect	Compliant		Non-compliant		Total	
	n	[% of 285]	*n*	[% of 285]	*n*	[% of 285]
I Insufficient	8	(2.8)	11	(3.9)	19	(6.7)
II Too strong/adverse						
a. intended/accidental			10	(3.5)		
b. adverse drug reactions	16	(5.6)			26	(9.1)
Total	24	(8.4)	21	(7.4)	45	(15.8)

Table 6. Agreement on the cause-effect relationship of drug related problems using two different sets of criteria

Criteria choosen for this study[a]	Cause-effect relationships according to: Criteria suggested in algorithm[b]							
	Definite		Probable		Possible		Total	
	n	%	n	%	n	%	n	%
Definite	2	(4.4)	0		0		2	
Probable	6	(13.3)	29	(64.4)	8	(17.8)	43	
Total	8	(17.8)	29	(64.4)	8	(17.8)	45	(100)

[a] cf. methods
[b] from reference 30–32

cally, nor by their plasma digoxin concentration (0.3–2.2 nmol/l).

The difficulties of evaluating ADRs have been demonstrated in two studies [21, 22], in which different clinical pharmacologists used their individual judgement to evaluate suspected events. In general, they disagreed as often as not. In one of these studies [21] the pharmacologists then discussed the cases and came to an "unanimous consensus" for each case [17]. An independent investigator then used standardized cause-effect criteria (adopted from 20) in a decision-table to evaluate the same cases. In 71% of the 60 cases the judgement based on the decision-table agreed with that of the consensus, and no events identified as *definite* or *probable* by the consensus or the algorithm were thought to be unrelated by the alternative evaluation [17]. We used the same set of cause-effect criteria (both from 20) for evaluating the drug-related problems. However, we had to adjust them slightly so that they also covered underdosage and non-compliance; e. g. in criterion No. 4, "dechallenge", the original text "– – – improvement on stopping the drug" [20] was changed to "– – – improved by dose adjustement, stopping or reinstitution of the drug therapy (cf methods)".

To check our cause-effect criteria a retrospective evaluation was made of the 45 patients according to a recently reported comprehensive and explicit algorithm for adverse clinical manifestations [30–32]. Absolute agreement between the two sets of criteria was found in 69% of cases (Table 6), and there were no major disagreements. According to our criteria, reappearance of the symptoms on repeated exposure to, or withdrawal of the suspected drugs (rechallenge), was needed to classify the cause-effect link as *definite*. As pointed out by Koch-Weser et al. [22], rechallenge is seldom possible or ethical. It also appears unnecessary in cases such as those with clearly toxic drug levels (No. 24), and congruence between drug concentrations and symptoms. These situations are better provided for in the new algorithm. However, derangement of preexisting clinical conditions, episodic reactions and reactions developing after withdrawal of the suspected drug might be underestimated by the algorithm.

There are seldom absolute answers in clinical studies of drug effects. Still, our results indicate that drug-related problems may be important in a significant number of admissions to medical clinics. Moreover, most of these problems seem to be related to irrational use of drugs.

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