Potential risks and prevention, part 2: Drug-induced permanent disabilities

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Abstract: Potential risk factors for and the preventability of drug-induced permanent disabilities were studied.

Case reports of adverse drug events (ADEs) published in *Clin-Alert* during 1978–97 were the source of information on drug-induced permanent disabilities. Patient, drug, and event variables were identified, and the causality, predictability, and preventability of each case were assessed. Data were entered into a relational database for analysis.

The data indicated 227 cases of drug-induced permanent disabilities. Twenty-three percent of the cases were assessed as definite, 47% as probable, and 30% as possible. Twenty-nine percent of the patients were less than 10 years old, and 36% were considered healthy. The drug categories most commonly associated with a drug-induced permanent disability were antimicrobials, vaccines, central-nervous-system agents, and antineoplastics. About half of the patients received more than the usual dosage. The most common permanent disabilities were brain damage, blindness, tardive dyskinesia, deafness, quadriplegia, and hearing loss. Event types were distributed as medication errors (55%), adverse drug reactions (43%), and drug interactions (2%). Eighty-four percent of the drug-induced permanent disabilities were judged to have been preventable; of these, a pharmacist could have prevented 40%. Litigation was reported for 56% of the cases of drug-induced permanent disability; judgments and settlements averaged $4.3 million.

A review of published case reports of ADEs for 1978–97 yielded information on possible risk factors for drug-induced permanent disabilities and on which events may have been preventable.

Index terms: Anti-infective agents; Antineoplastic agents; Central nervous system drugs; Dosage; Drug interactions; Drugs, adverse reactions; Errors, medication; Pharmacists; Toxicity; Vaccines

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This report is the second in a series of four describing significant adverse drug events (ADEs), including adverse drug reactions (ADRs), medication errors, allergic drug reactions, and drug interactions.[1-3] The present study was conducted to generate hypotheses about what may contribute to drug-induced permanent disabilities and to discover whether these tragic events can be prevented.

The frequency of drug-induced permanent disabilities is unknown. A literature search with the terms "drug-induced and permanent disability" and "drugs and disability" failed to find any references on this subject. There are a few reports of specific drugs causing a specific permanent disability and some reviews of specific drug-induced disabilities (e.g., drug-induced dementia),[4-6] but there are no epidemiologic studies of the incidence, prevalence, or risk factors for drug-induced permanent disabilities. The public is becoming more aware of the problem of ADEs, however, as shown by the 1999 publication of a report on medication errors by the Institute of Medicine.[7]

The objectives of this study were to (1) identify case reports of drug-induced permanent disabilities, (2) develop a relational database of these events, (3) analyze the database for trends, (4) identify potential risk factors, and (5) identify events that may have been preventable, including those that may have been prevented by a pharmacist.

Methods

The methods used in this study were identical to those in the study described in part 1.[1] A drug-induced permanent disability was defined as a

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permanent change, harm, damage, or disruption in the patient's body function or structure, physical activities, or quality of life that in all likelihood was caused by a drug.

Event variables included the drug-induced disability and whether there was any recovery. The permanent disability was classified as total—grave (e.g., quadriplegia, severe brain damage, mental retardation, need for lifelong care, need for transplantation, fatal prognosis), total—major (e.g., paraplegia, blindness, loss of two limbs, brain damage), partial—major (e.g., deafness, loss of one limb, loss of one eye, loss of one kidney, loss of fertility, palsy, confinement to a wheelchair, hemiplegia, balance problems), or partial—minor (e.g., loss of a finger, loss of or damage to organs, acute renal failure, partial blindness, partial hearing loss, tardive dyskinesia, memory loss).[8]

Table 1.
Age of Patients with Drug-Induced Permanent Disabilities (PDs) (*n* = 200)

Age (yr)[a]	No. (%) PDs
<10	58 (29.0)
10–19	10 (5.0)
20–29	26 (13.0)
30–39	20 (10.0)
40–49	31 (15.5)
50–59	20 (10.0)
60–69	26 (13.0)
>69	9 (4.5)

[a]Mean ± S.D. age, 32.2 ± 24.1 years.

Results

Reports. The reports ranged over a 20-year period from 1978 to 1997. The prepared data reflected 227 cases involving a permanent drug-induced disability. Drug-induced permanent disabilities represented 4% of all *Clin-Alert* reports over the period. The primary sources of the reports were legal journals (56%) and medical journals (43%); pharmacy journals accounted for 1%. Most of the reports were from North America (78%) and Europe (17%).

Causality. Twenty-three percent of the disabilities were assessed as definite, 47% as probable, and 30% as possible. Nine percent of ADRs represented type A reactions and 91% type B reactions.

Patients. The mean ± S.D. age of the patients was 32.2 ± 24.1 years (range, <1 to 81 years) (Table 1). Twenty-nine percent of the patients were less than 10 years old. A majority of the patients (53%) were female. No primary diagnoses were prominent. In cases in which the severity of illness was known, 36% of the patients were healthy, 38% were moderately ill, 21% were severely ill, and 4% were terminally ill.

Drugs. Most of the drugs (83%) were used for indications listed in *AHFS Drug Information*.[9] Antimicrobials, central-nervous-system agents, antineoplastic agents, and vaccines accounted for 59% of the permanent disabilities. The drugs and vaccines most commonly suspected of inducing a threat to life represented 34% of the drugs reported for the 227 cases. Table 2 lists the drugs by type of event.

Almost half of the patients who had a permanent disability received more than the usual dosage (Table 3). Replacement preparations, hormones, antimicrobial agents, and central-nervous-system agents accounted for most of the cases in which a dosage exceeded the usual dosage. Administration by injection was the route used most often (63%). However, other routes were the ones most often associated with more-than-usual dosages.

Drug levels could have been monitored in 54 cases (24%), but monitoring occurred in only 11 (20%) of these cases. In these cases, the drug level was either high (9%) or very high (91%).

When the location where the drug was started was known, most patients (57%) received the drug while in a hospital; 38% were outpatients, and 5% were in other locations. Most of the disabilities took place within a month of the start of therapy, with 45% occurring during the first 24 hours (Table 4).

Events. Table 5 lists the most common drug-induced permanent disabilities identified. Of the permanent disabilities, 22% were total—grave, 18% were total—major, 20%

Table 2.
Drugs and Mechanisms Most Commonly Suspected of Inducing Permanent Disabilities[a]

Adverse Drug Reaction	Allergy	Error	Interaction	All[b]
Cisplatin	None	Doxorubicin	Cimetidine	Diphtheria and tetanus toxoids and pertussis vaccine
Diphtheria and tetanus toxoids and pertussis vaccine		Gentamicin	Clarithromycin	Theophylline
Methotrexate		Lithium	Ergotamine	Gentamicin
Measles, mumps, and rubella vaccine		Neomycin	Erythromycin	Cisplatin
Polio vaccine		Oxytocin	Fluorouracil	Methotrexate
Tamoxifen		Potassium chloride	Levamisole	Potassium chloride
Vigabatrin		0.9% sodium chloride injection	Phenytoin	Measles, mumps, and rubella vaccine
		Corticosteroids	Propranolol	Polio vaccine
		Theophylline	Ticlopidine	Neomycin
			Verapamil	Oxytocin

[a]Listed in order of decreasing frequency.
[b]All drugs causing permanent disabilities by all mechanisms.

were partial—major, and 39% were partial—minor (Table 6). Over 48% of the events involved the nervous system, 19% involved the eyes, and 11% involved the ears. The most common events were brain damage, blindness, and tardive dyskinesia. In 30% of the cases, the diagnosis of a drug-induced permanent disability was made after the drug was discontinued. Only 16% of patients had some recovery from their disability.

Mechanisms. The mechanisms of drug-induced permanent disabilities were medication errors (55%), ADRs (43%), and drug interactions (2%). There were no allergic drug reactions. Twenty-three percent of the ADRs were associated with the use of antineoplastic agents and 19% with vaccines. Nineteen percent of the errors were associated with the use of antimicrobials; 13% with electrolyte, caloric, and water-balancing agents; and 9% with antineoplastic agents.

Drug interactions. There were five drug interactions. Two of the five interactions were unclassified events, two were category 3 events, and one was a category 2 event (Table 7).[10]

Medication errors. Of the medication errors identified in this study, 57% were prescribing errors. In 29% of the errors, patients had been prescribed the wrong dosage, in 19% the drug was considered a poor choice, and in 19% the monitoring was considered poor. Mistakes accounted for 72% of the errors, while 28% were slips. Inattentiveness accounted for 41% of the slips. Although the data were limited, it appeared that a fair amount of the medication associated with a permanent disability was provided in the outpatient, pediatric, and operating-room areas of hospitals.

Lawsuits. Lawsuits with financial judgments were reported in 56% of the cases of drug-induced permanent disability. Defendants in these cases were physicians (32%), multiple parties (22%), hospitals (19%), and other (27%). The most common reasons for bringing suit were overdose (22%), improper treatment (19%), and poor or no monitoring (19%). A jury decided 59% of the cases. Judgments and settlements ranged from $20,000 to $127 million (mean ± S.D., $4.3 million ± $14 million).

Prevention. Nearly 84% of the drug-induced permanent disabilities could have been prevented, and of these, 40% could have been prevented by a pharmacist (Table 8). Better patient monitoring before and during therapy may have prevented many of the drug-induced disabilities (Table 9). Computer screening of orders may have prevented 11%.

Table 3.
Dosages Used in Cases of Drug-Induced Permanent Disability (PD) (*n* = 111)

Dosage	No. (%) PDs
Below usual	8 (7.2)
Usual[a]	48 (43.2)
Two to three times usual	17 (15.3)
More than three times usual	38 (34.2)

[a]As listed in reference 9.

Table 4.
Onset of Permanent Disabilities (PDs) after Initiation of Suspected Drug (*n* = 170)

Time of Onset (Days)	No. (%) PDs
<1	77 (45.3)
1–7	22 (12.9)
8–31	18 (10.6)
32–365	28 (16.5)
>365	25 (14.7)

Table 5.
Drug-Induced Permanent Disabilities (*n* = 227)

Permanent Disability	No. (%)
Brain damage	42 (18.5)
Blindness	8 (3.5)
Tardive dyskinesia	8 (3.5)
Deafness	7 (3.1)
Quadriplegia	7 (3.1)
Hearing loss	7 (3.1)
Paraplegia	6 (2.6)
Vision loss	6 (2.6)
Neuropathy	6 (2.6)
Gangrene	5 (2.2)
Cataracts	5 (2.2)
Poliomyelitis	5 (2.2)
Renal failure	5 (2.2)
Ototoxicity	5 (2.2)
Other	105 (46.3)

Table 6.
Drug-Induced Permanent Disabilities (PDs) by Severity (*n* = 224)

Severity[a]	No. (%) PDs
Total—grave	50 (22.3)
Total—major	41 (18.3)
Partial—major	45 (20.1)
Partial—minor	88 (39.3)

[a]Defined in reference 8.

Discussion

The patients in this study who had a drug-induced permanent disability were mostly young and relatively healthy. Many of the patients were less than 10 years old. Antimicrobials, vaccines, central-nervous-system agents, and antineoplastics were the categories of drugs most often suspected of causing a permanent disability. Errors in prescribing, poor drug selection, overdose, and poor monitoring were often identified. The drugs most commonly suspected of inducing a permanent disability varied by type of ADE. Almost half of the patients received more than the usual dosage of the suspected drug, and over half were victims of an error.

The most common errors involved prescribing, and most of these involved a mistake rather than a slip. The most common prescribing errors involved selecting an inferior drug, prescribing too much drug, and poorly monitoring the patient. These problems were reflected in the reasons for the litigation.

What criteria should be used for selecting patients for monitoring? Although practitioner autonomy is important, there is something to be said for an organized approach by pharmacists practicing in one setting. Agreement on screening criteria and medical staff knowledge (by the pharmacy and therapeutics and patient care committees) is important. So is the routine reporting of results that will garner more support and the approval of future clinical pharmacy endeavors.

The results suggest that children less than 10 years old should be carefully monitored, along with patients receiving drugs implicated in the cases of permanent disability. It would also be wise to be especially vigilant during the first 24 hours of therapy and always to measure serum drug levels if the drug can be monitored pharmacokinetically.

The best prevention strategies against drug-induced permanent disabilities may be employing patient-focused pharmacists who are available when and where the drug is prescribed and programming computers to screen for danger. All health care computer systems should be able to screen for overdoses, drug interactions, and contraindications and to alert the pharmacist when a laboratory test is needed.

Although there were only five drug interactions associated with the permanent disabilities in this study, the results resemble those of the study on fatal ADEs.[1] None of the drug interactions were category 1 interactions, two were in category 3, and two were unclassified. Further study is needed to determine why the interactions in this study were not classified as more serious.

Several potential risk factors demand further study by using more rigorous epidemiologic methods to discover their contribution to drug-induced disabilities. The most recent controlled study of risk factors for ADEs in hospitalized patients found that ADEs occurred more frequently in sicker patients who stayed in the hospital longer.[11] However, after adjusting for level of care and preevent length of stay, few risk factors emerged. The study focused on ADEs

Table 7.
Drug Interactions Suspected of Contributing to Permanent Disabilities (PDs) (*n* = 5)

Severity Level (No. PDs)[10]	Definition	Object Drug	Participant Drug
Category 1 (0)	Avoid combination. Risk always outweighs benefit.	. . .	. . .
Category 2 (1)	Usually avoid combination. Use combination only under special circumstances.	Clarithromycin	Ergotamine
Category 3 (2)	Minimize risk. Take action as necessary to reduce risk.	Verapamil Ticlopidine	Propranolol Phenytoin
Category 4 (0)	No action needed. Risk of adverse outcomes appears small.	. . .	. . .
Category 5 (0)	Evidence suggests no interaction.	. . .	. . .
Unclassified (2)	Not listed.	Fluorouracil Erythromycin	Levamisole Cimetidine

Table 8.
Preventability of Drug-Induced Permanent Disabilities (PDs) (*n* = 200)

		No. (%) PDs	
Patient Status	No. % Patients	Preventable	Preventable by Pharmacist
Relatively healthy	73 (36.5)	51 (69.9)	19 (37.3)
Moderately healthy	77 (38.8)	70 (90.9)	29 (41.4)
Severely ill	42 (21.0)	37 (88.1)	15 (40.5)
Terminally ill	8 (2.0)	8 (100.0)	3 (37.5)

Table 9.
Possible Mechanisms for Preventing Drug-Induced Permanent Disabilities (PDs) (*n* = 227)

Mechanism	No. (%) PDs
Better patient monitoring	35 (15.4)
Computer screening	25 (11.0)
Improved laboratory test monitoring	20 (8.8)
Physician education	17 (7.5)
Patient risk assessment	16 (7.0)
Double-checking	12 (5.3)
Nurse education	10 (4.4)
Earlier discharge	9 (4.0)
Other	83 (36.6)

in general, not just drug-induced permanent disabilities. In addition, only a few risk variables were analyzed.

The limitations of this study are similar to those listed for the study described in part 1.[1] Despite the limitations, until further study is undertaken, the results can be used by pharmacists to help screen for patients who may be at risk for drug-induced disabilities.

The drug interactions reviewed in this study need closer scrutiny, and there is a need for better guidelines on how to prepare a case report on a drug-induced permanent disability.

Conclusion

A review of published case reports of ADEs from 1978 to 1997 yielded information on possible risk factors for drug-induced permanent disabilities and on which events may have been preventable.

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