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Commentary

Adverse drug reactions—a matter of opinion

The accurate identification of adverse drug reactions (ADRs) is difficult because ADRs usually present no unique clinical or laboratory findings that demarcate them from the manifestations of concurrent illnesses. The identification of ADRs depends on the clinical assessments of physicians–sometimes the clinician treating the patient and at other times a clinical pharmacologist. Considering the complex and subjective nature of clinically identifying ADRs, how accurately are ADRs identified? To answer this question, three clinical pharmacologists each independently evaluated 60 selected cases to determine if medication, alcohol, or "recreational" drugs had caused the hospitalization. The three clinical pharmacologists agreed on only 30 cases (50%), and 27 of these were thought to be unrelated to medications. In 19 of the 30 cases about which the clinical pharmacologists disagreed, they disagreed on whether or not a medication- or alcohol-related event had occurred at all. The clinical pharmacologists disagreed with the physicians treating the patient in 22% to 37% of the cases, but because of the differences among the pharmacologists, the treating physicians agreed with at least one of them in 95% of the cases. Complete agreement between the clinical pharmacologists and the treating physicians occurred in 47% of the cases. This degree of disparity in the clinical identification of ADRs shows that the evaluation of ADRs is subjective and imprecise. The accurate identification of ADRs awaits the development of an objective technique for recognizing ADRs.

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Adverse drug reactions (ADRs) are an important problem in therapeutics, and several studies have attempted to assess the magnitude and impact of ADRs in clinical practice.[1, 6–8] Some of the data collected in these investigations have been extrapolated to the national population with journalists proclaiming "thousands a year killed by faulty prescriptions."* However, review of the literature on which such claims are based reveals that the data presently available are an inadequate basis for estimating the magnitude of the ADR problem.[3, 4]

One of the major difficulties in evaluating ADRs is the subtle and often complex nature of the clinical manifestations of an ADR, which must be extricated from the clinical features of one or more concurrent illnesses. As Feinstein pointed out: "After we work our way through all the majesty of the computer print-out and the glory of the statistics, we find that the decision-making mechanism for identifying adverse reactions . . . depends on the vagaries of clinical judgment of an array of unstandardized physicians."[2]

Some studies have utilized the assessment of admitting physicians[6] who presumably had no special training or experience in assessing ADRs, while other studies have used clinical pharmacologists to identify ADRs.[8] One might expect that a clinical pharmacologist would have little difficulty in assessing a suspected ADR. Yet ADRs generally present no unique identifying features even for the expert clinical pharmacologist, and identifying a single responsible drug from several possible candidates may be impossible.

The purpose of this investigation was to examine the assessment of ADRs by several clinical pharmacologists, each evaluating the clinical situation independently, and to compare their evaluations with the impressions of the attending and house physicians who had treated the patients.

Methods

Patients were randomly selected from those admitted to Strong Memorial Hospital through the Emergency Department between June 22 and August 5, 1975. The patients were interviewed by one of the investigators (C. L. S.) shortly after admission, and a complete drug history, including the use of over-the-counter medication, alcohol, and "recreational" drugs, was recorded on special data sheets. Information on patient compliance was specifically noted for each prescribed medication. Each patient's past medical history, history of the present illness, physical findings, laboratory data, and hospital course, including therapy, were recorded from the patient's hospital chart. In addition, separate notation was made as to whether in the opinion of the attending or house physician the patient's hospital admission was related to the use of medications, alcohol, or recreational drugs. When admission was thought to be drug-related, an attempt was made to identify the responsible drug, and the circumstances were classified as accidental poisoning, suicide attempt, noncompliance, or ADR. Further, the certainty of the association between the suspected drug and the untoward clinical event was classified as definite, probable, or possible.

Out of 186 cases collected, 60 were selected for detailed study. They included all cases in which the attending or house physician had suspected that the hospitalization might be realted to medication, alcohol, or recreational drug use, including cases in which the responsible physicians' final decision was that the hospitalization was unrelated to these agents. In addition, several cases were included in which no medication, alcohol, or recreational drug had been suspected by the treating physicians as a cause of hospitalization.

The compiled data for the 60 cases (excluding attending and house physician evaluations) were then independently evaluated by three clinical pharmacologists who were asked to determine whether each patient's hospitalization was caused by accidental poisoning, suicide attempt, noncompliance, alcohol, recreational drugs, or an ADR. They were asked to assess the certainty of any positive decision as definite, probable, or possible, and to indicate the specific drug(s) responsible for any ADR

*Rensberger, B.: New York Times, Jan. 28, 1976.

Table I. *Disagreement among clinical pharmacologists on the cause of admission to the hospital*

Area of disagreement	*No. of cases*	
Certainty of relationship		5
Probable vs Definite ADR	(1)	
Possible vs Probable ADR	(1)	
Possible vs Definite alcohol	(1)	
Probable vs Definite alcohol	(2)	
Relationship of agent to untoward event		19
Unrelated vs Definite ADR	(1)	
Unrelated vs Possible ADR	(6)	
Unrelated vs Noncompliance	(7)	
Unrelated vs Definite alcohol	(2)	
Unrelated vs Probable alcohol	(1)	
Unrelated vs Possible Alcohol	(2)	
Responsible agent		4
Other		2
Accidental poisoning vs Suicide attempt	(1)	
Noncompliance vs Possible ADR	(1)	
Total		30

Results

Evaluation by clinical pharmacologists. The three clinical pharmacologists independently reached the same conclusion in 30 cases (50%). The evaluations of these cases were: definite alcohol, 3; suicide attempt, 2; possible ADR, 1; unrelated to medications, alcohol, or recreational drugs, 24.

Of the 30 cases on which the pharmacologists disagreed, 5 involved minor disagreements on the certainty of the link between the agent and the reaction, and 19 involved major disagreements as to whether or not any agent was implicated as a cause of hospitalization (Table I). The range of divergence in one case was so extreme that one clinical pharmacologist believed that no ADR had occurred while another believed that it was a definite ADR. In two cases alcohol was though to be a definite cause of admission by at least one clinical pharmacologist, while another thought alcohol was not even a possible cause of admission. Interestingly, the physician who believed that alcohol was definitely implicated in one case, thought it was unrelated in the other case.

Table II. *Agreement between treating physicians and clinical pharmacologists*

Clinical pharmacologists	*Treating physicians*	
	*Agree**	*Disagree*
A	47 (78)	13 (22)
B	38 (63)	22 (37)
C	43 (72)	17 (28)
A, B, *and* C	28†	3 (5)
A, B, *or* C	57 (95)	—

*Number of cases; percent in parentheses.

†N. B.: There were only 30 cases about which A, B, and C agreed among themselves, and the treating physicians concurred in 93% of these 30 cases, or 47% of the total cases.

There were four cases in which the clinical pharmacologists disagreed on the responsible agent. In each of these cases the patient had taken several drugs (e.g., ethanol, diazepam, and meprobamate), any of which might have been responsible for the untoward event.

In the two remaining cases the disagreement concerned the circumstances of the drug use. In one case the question was whether or not the patient had intended to harm himself (accidental poisoning vs suicide attempt), and the other, whether the patient had taken more than the prescribed dose of medication (noncompliance vs possible ADR).

Evaluation by attending and house physicians. The treating physicians disagreed with the individual clinical pharmacologists in 22% to 37% of the cases (Table II). They agreed with at least one of the pharmacologists in 57 of the 60 cases (95%), with the three cases of disagreement involving minor discrepancies in the certainty of the link between the agent and the reaction (e.g., probable vs definite).

Discussion

The three clinical pharmacologists agreed on only 50% of the cases, and only one of these was thought to involve an ADR. There were 25 cases that at least one evaluator designated as drug-related, and the three clinical pharmacologists agreed on only 3 of these (2 suicide attempts and 1 possible ADR). Further, in 14 of these cases (56%) they disagreed among themselves on whether or not the hospitalization was

drug-related at all. There were 15 cases in which at least one evaluator thought the hospitalization might have been due to an ADR. The three clinical pharmacologists disagreed on 14 of these cases (93%), and in 8 cases (53%) there were major disagreement on whether or not an ADR might have been responsible. In 4 of these 15 cases (27%) the experts disagreed on the drug responsible for the ADR. Although this degree of divergence may have been unique to this group of evaluators, Koch-Weser and Greenblatt have reported similar results.[5]

The group was only slightly more concordant in evaluating hospital admissions related to alcohol. The three clinical pharmacologists concurred in the belief that alcohol was at least possibly responsible for hospitalization in 6 of 11 cases (55%) where at least one evaluator thought alcohol had been implicated.

The attending and house physicians agreed with at least one of the clinical pharmacologists in 95% of the cases, but disagreed with the individual clinical pharmacologists in 22% to 37% of the cases. Some of the differences of opinion between the treating physicians and the clinical pharmacologists might have been due to differences in the information available for making the evaluations. The clinicians might have been aware of pertinent data not recorded in the charts, while the clinical pharmacologists often had more detailed drug histories available. Considering the broad range of responses among the clinical pharmacologists, it is impossible to draw many conclusions, but the attending and house physicians appeared to agree with the three clinical pharmacologists about as often as the clinical pharmacologists agreed among themselves.

The study demonstrates the enormous difficulty in assessing ADRs. There are few distinct clinical findings or laboratory results that demarcate an ADR from the manifestations of a patient's underlying illness. The tolerance range for identifying ADRs in clinical practice is so coarse that neither treating physicians nor clinical pharmacologists agree on most cases. There is presently no objective methodology for operationally identifying ADRs in a consistently reproducible fashion. Until such methodology is developed, the evaluation of ADRs will remain subjective and imprecise.

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