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DIFFICULTIES IN ASSESSING THE ADVERSE EFFECTS OF DRUGS

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1 In recent years the phenomenon of the adverse drug reaction (ADR) has become a focus of increased attention and research, and we have become aware of the clinical complexity of the phenomenon and some of the difficulties inherent in assessing adverse effects. Evidence for such difficulties includes the discrepancies in figures for ADR incidence in epidemiological studies, the non-specificity and suggestibility of ADR symptoms, and the substantial disagreements, even among experts, in the diagnosis of ADRs.

2 An observed clinical manifestation heavily depends on the clinical setting and on the intent of the clinician, and the large number of factors that may confound the link between a given manifestation and an administered drug. A diagnostic algorithm, or branched logic decision format, has recently been developed. It comprises six axes of decision strategy and provides standardized, operational rules for rating the probability of an ADR.

Introduction

THE notion that treatment for a disease can do harm as well as good doubtless long pre-dates Hippocrates' oath of '*primum non nocere*'. The history books are filled with terrifying accounts of magic cures and potions; in fact, the more horrible, the fouler smelling, the more revolting the remedies, the more impressive and, in some cases, the more effective they seemed to be. And some of these remedies are of more recent vintage than we might like to recall. Crocodile dung, unicorn horn, and Egyptian mummy may date from ancient times, it is true, but bleeding, blistering, purging, and puking were very much in vogue until a mere hundred years ago.

The past century, and especially the past few decades, has witnessed the birth of clinical pharmacology and the introduction of an overwhelming number of pharmaceutical agents. The fact that we are convinced that today's drugs are more effective, if less dramatic, modes of treatment than some of history's colourful therapies should not blind us to the possible detrimental effects of these potent agents. We can no longer consider efficacy without contemplating safety. The thalidomide disaster of the early 1960s, the rise of consumerism, and the present furor over malpractice have all contributed to the increasing recognition of the phenomen of the adverse drug reaction (ADR).

The past ten years especially has seen a burgeoning interest in and writing about ADRs, with articles now common in both the medical and lay press. ADRs have been reported to be a significant cause of inpatient (Schimmel, 1964; Seidl, Thornton, Smith & Cluff, 1966; Borda, Slone & Jick, 1968; Hurwitz & Wade, 1969) and outpatient (Kellaway & McCrae, 1973; Apriet *et al.*, 1977) morbidity, hospital admission (Hurwitz & Wade, 1969; Caranasos, Stewart & Cluff, 1974; Miller, 1974), and even death (Schimmel, 1964; Hurwitz & Wade, 1969; Caranasos *et al.*, 1974; Porter & Jick, 1977). ADRs have also been blamed for prolonged hospitalizations and for adding billions of dollars to annual health care expenditures (Talley & Laventurier, 1974). Amid these many reports and contentions, the diagnosis of an ADR has usually depended on unspecified and unstandardized clinical judgment, arising from the subjective impression and previous experience of individual clinicians (Feinstein, 1974). No scientific procedures have been available for assessing whether an observed adverse event is actually an ADR. Thus clinicians, pharmacologists or others wishing to make such an assessment have usually had to rely on published 'laundry lists' in which ADRs are enumerated without rigorous examination of the data upon which such lists are based.

The difficulty with the diagnosis of ADRs is that they represent exceedingly complex clinical phenomena. We cannot continue to avoid this problem if we wish to develop more objective and reliable procedures for assessing ADRs; we must be willing to confront it directly. The purpose of this article is to describe the pathogenesis of the problem as well as to address an approach to its treatment. I will begin by discussing several lines of evidence documenting how complex and difficult the assessment of ADRs really

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is. My next step will be to examine the source of the difficulty by attempting to dissect out the numerous factors complicating the identification of ADRs. I will then conclude with a presentation and discussion of a method of standardized assessment that my colleagues and I have developed for sorting out these difficult factors.

The evidence

I have been stressing the complex, difficult judgments necessary in the identification of ADRs. Lest this position be taken to represent one person's exaggerated, overstated reaction, let us examine three lines of evidence that, in my opinion, lend support to the contention. These three areas can be categorized as follows: (1) discrepancies in the incidence of ADRs reported in epidemiological studies; (2) the non-specificity and suggestibility of symptoms attributed to ADRs; and (3) interobserver disagreement among experts in the diagnosis of ADRs.

Numerous studies of the epidemiology of ADRs have appeared in the medical literature in recent years. These studies have sought to define the scope of the ADR problem by determining incidence rates in certain populations. As an illustration of the wide discrepancies in incidence figures reported, let us focus on hospitalized patients, because it is in the hospital setting that most of the studies of ADR epidemiology have been carried out.

Table 1 summarizes several studies reported over a 12-yr period bearing on the incidence of ADRs in inpatients. Various authors report anywhere from 1.5% to 35% of such patients developing ADRs while in the hospital. This enormous, 20-fold discrepancy is caused by three major factors: (1) differences in intensity of surveillance; (2) differences in definitions of ADRs and criteria for evaluating them; and (3) differences in the populations studied.

By examining the three columns in Table 1 containing the plus and minus signs, we can discern some definite trends in the figures. Those studies that incorporate active surveillance techniques, use broad definitions and criteria, and restrict themselves to adult medical patients, such as those of the Boston Collaborative Drug Surveillance Program (Borda, Slone & Jick, 1968), report the highest figures. By actively monitoring for adverse events possibly caused by drugs, by not attempting to define the probability of the causal role of the drugs in these adverse events, and by restricting their surveillance to acutely ill, adult medical patients, they uncover an alarmingly high incidence rate for ADRs.

At the other extreme, those studies with more 'passive' monitoring procedures, stricter definitions and criteria, and a more general hospital population including non-medical hospital patients, such as those of Wang & Terry (1971), report the lowest incidence figures. Thus, from this line of evidence, if we were to ask the question: How often do ADRs occur?, the response would have to be: It depends. It depends on how intensively one searches, it depends on what one means by an ADR, and it depends on the group of people in whom one looks.

Another problem with the diagnosis of ADRs is the type and severity of the adverse clinical manifestation. Table 2 lists the most common symptoms attributed to ADRs; this list accounts for about two-thirds of ADRs in most studies. Obviously there is nothing specifiic about these symptoms that would alert a physician to the occurrence of an ADR in his or her patient. In fact, up to 80% of healthy patients on no medication have been shown to report similar symptoms (Reidenberg & Lowenthal, 1968).

Table 2 Common symptoms of ADRs

Nausea/vomiting
Diarrhoea
Abdominal pain or discomfort
Rash
Pruritus
Drowsiness
Insomnia
Weakness
Headache
Dizziness
Tremulousness
Muscle twitching
Fever

Table 1 The incidence of ADRs in hospital inpatients

Study	*Incidence (%)*	*Active surveillance*	*Broad definitions*	*Restriction to medical patients*
Schimmel (1964)	11.1	−	+	+
Seidl *et al.* (1966)	13.6	+	−	+
Ogilvie & Ruedy (1967)	18	−	+	+
Borda *et al.* (1968)	35	+	+	+
Hurwitz & Wade (1969)	10.2	+	+	−
Gardner & Watson (1970)	10.5	+	−	+
Wang & Terry (1971)	1.5	−	−	−
Smidt & McQueen (1972)	3.0	−	+	−
Vakil *et al* (1975)	19.8	+	+	+

To further complicate the matter, the percentage of patients with symptoms and the number of symptoms per patient both rise with placebo administration (Green, 1964). And many studies have documented the increased reporting of symptoms when patients are specifically asked about such symptoms, as opposed to merely being asked how they feel (Avery, Ibelle, Allison & Mandell, 1967; Downing, Rickels & Meyers, 1970). This kind of information emphasizes another important caveat in our interpretation of the ADR literature: the lack of control data tends to overestimate the incidence of ADRs.

What about the experts, the clinicial pharmacologists? Can they agree in diagnosing ADRs? Karch *et al.* (1976), at the University of Rochester, have reported a study of the interobserver disagreement among experts in the assessment of ADRs. Three clinical pharmacologists differed vastly in their opinions as to the role of ADRs in causing emergency room hospital admission in a series of 60 cases. Similarly, Koch-Weser, Sellers & Zacest (1977), at the Massachusetts General Hospital, have noted major disagreements when three clinical pharmacologists were asked to assess the probability of ADRs in 500 suspected cases.

So the experts do not seem to agree either. What is it about the phenomenon of the ADR that renders its diagnosis so difficult, even for experts? The next section examines the sources of difficulty in assessing the adverse effects of drugs.

Sources of difficulty

Before a given clinical manifestation or event can be labelled an ADR, there are two separate requirements that should be met: (1) the event must, in fact, be 'adverse'; and (2) a drug must be demonstrated, within 'reasonable' likelihood, to be the cause.

The first of these requirements is a matter of definition. Differences in opinion about whether or not an observed event is indeed adverse can be a major source of difficulty in the diagnosis of ADRs. Side-effects can span the range from useful indicators, to harmless epiphenomena, to innocuous nuisances, to harmful injury, and of course even to death. Leaving aside for a moment the question of the drug's true role in causation of such side-effects, any decision about the presence or absence of an ADR will surely depend on how one rates the observed event on this 'adversity scale'.

As a further complication, a given type of event may not have a fixed location on this 'scale', because the degree of adversity may depend to a great extent on the clinical setting in which the event occurs. As an illustration of this point, consider the leukopenia that can occur as a result of cyclophosphamide administration. Normally we would consider the development of leukopenia in a patient as an adverse event. In the setting of a patient with a serious malignancy, however, leukopenia can be a very helpful indicator of dosage tolerance and requirements in the hands of an experienced chemotherapist. As another example, the dry mouth that so frequently occurs as a side-effect of tricyclic antidepressant therapy might well be considered an annoying adverse effect by the patient,but his psychiatrist might use this side-effect as a very helpful indicator of appropriate dosage for that patient.

The World Health Organization (WHO, 1970) has defined an ADR as: 'Any response to a drug which is noxious and unintended and which occurs at doses used in man for prophylaxis, diagnosis, or therapy.' As this definition requires a judgment both about noxiousness (the iocation, if you will, on our adversity scale) as well as intent, it is not surprising that even though many clinical pharmacologists, epidemiologists, and regulatory agencies accept and use the WHO definition, it none the less allows considerable room for disagreement.

The second major source of difficulty in the diagnosis of ADRs is, as mentioned above, the judgment as to the causal role of a drug in the development of the adverse event. Even if different observers could agree on the adversity of the event, they might disagree quite substantially on the likelihood that a drug in general, or any specific drug in particular, was responsible for causing this event.

Let us examine what happens when a person is given a drug. As outlined by Feinstein (1974), this clinical setting contains three elements: the person, the drug, and the event. Each of these three elements may admit of a number of factors that may make it extraordinarily difficult to ascertain the role of the drug in causing the event. Personal factors include demographic background, basic underlying clinical state, comorbid features, and intercurrent illnesses. The suspected drug may not be the only manoeuvre involved. Other drugs, drug interactions, non-drug therapeutic modalities (for example, radiation therapy), and diagnostic tests and procedures can all lead to adverse events. Finally, the timing of the event may be confusing, or the event might be transient and episodic, irreversible, or a common, everyday occurrence that might well occur spontaneously.

Table 3 lists the difficult factors that I and others have found to be most troublesome in establishing the all-important causal link between an observed untoward clinical manifestation and a suspected drug. What is needed is a set of standardized operational criteria for sorting out these factors. In an initial attempt at establishing such criteria, Irey (1972) has provided operational definitions for five ordinal categories for noting the probability of an ADR. More recently, Karch & Lasagna (1977) have developed a

Table 3 Difficult factors in establishing the causal link in ADRs

Recently introduced drug
Multiple drugs
Drug withdrawal
Drug interaction
Non-drug therapies
Diagnostic tests and procedures
Underlying illnesses
Intercurrent illnesses
Timing of events
Common, spontaneous events
Transient, episodic events
Irreversible events
Tolerance
Specific treatment clouding dechallenge
Prophylactic treatment clouding rechallenge

decision table in which the diagnosis of an ADR depends on judgments about alternative aetiologic candidates, previous experience with the drug, timing, dechallenge, and rechallenge. These studies were of enormous benefit in focusing attention on the need for assessing the causal link between drug and event, and thus in improving the quality of data in epidemiological studies and drug surveillance activities. Though outlining the major areas of complexity, however, these two approaches supplied no specific criteria for the judgments required, and the reproducibility of such judgments was not examined.

Expanding from this previous work, my colleagues and I have developed and tested a set of diagnostic criteria that provide specific, operational rules for ADR assessments (Kramer, Leventhal, Hutchinson & Feinstein, 1979; Hutchinson *et al.*, 1979). The criteria are arranged as an algorithm, or branched logic decision format, from which emerges an ordinal probability for the diagnostic likelihood of an ADR. For reasons of convenience in practical usage, we have developed a questionnaire that is the exact logical equivalent of the algorithm. The following section presents an outline and brief discussion of this recently developed procedure.

An algorithm for the operational assessment of ADRs

Before presenting the details of the algorithm itself, some definitions will be required. The algorithm is directed only at the second type of difficulty outlined in the previous section, namely, the establishment of the strength of the causal link between an administered drug and some observed untoward clinical event. It does not provide a mechanism for judging the adversity of the event itself. As discussed above, that judgment is so dependent on the clinical setting and on the intent of the treating physician, that no universally applicable rules for making it can, or should, be attempted. The decision that an event is adverse must, therefore, remain entirely separate and must be made *de novo* for each suspected case.

Leaving aside, then, the definition of 'adverse', there remains a need to define what we mean by 'adverse drug reaction'. Though useful as a general, theoretical concept, the WHO definition, as we have seen, depends too heavily on the intent of the treating clinician to be helpful in the practical task of operationally assessing potential adverse drug reactions. My colleagues and I have defined an untoward clinical manifestation (CM) as 'an abnormal sign, symptom, or laboratory test, or a cluster of abnormal signs, symptoms, and tests' and an ADR as 'an undesirable clinical manifestation consequent to and caused by the administration of a given drug' (Kramer *et al.*, 1979). Our ADR algorithm is designed to rate the probability that the CM in fact represents an ADR.

The algorithm comprises six axes, or areas, of decision strategy (see Table 4):

Table 4 ADR algorithm: axes of decision strategy

I.	Previous general experience with the drug
II.	Alternative aetiological candidates
III.	Timing of events
IV.	Drug levels and evidence of overdose
V.	Dechallenge
VI.	Rechallenge

Axis I: Previous general experience with the drug This first axis considers the questions of how long the suspected drug has been in use, whether or not the observed CM has ever been reported with the suspected drug, and whether or not it has been widely known to occur as a consequence of the drug's administration.

Axis II: Alternative aetiologic candidates The purpose of this axis is to weigh the relative merits of other possible causes of the CM, such as underlying illnesses, new illnesses, non-drug therapeutic modalities, and diagnostic tests and procedures. Also considered is the likelihood of the CM's being a common phenomenon that often occurs spontaneously without any recognizable cause.

Axis III: Timing of events In this axis, the probability of an ADR is rated according to the time of appearance of the CM relative to the administration of the suspected drug.

Axis IV: Drug levels and evidence of overdose For dose-related types of CMSs, this axis assesses drug levels (when available and known) and other evidence (for example, a newly empty pill bottle or the nurse's charting of an administered drug at an erroneous dosage) of drug overdosage.

Axis V: Dechallenge This long and complicated axis, which is subdivided into three smaller axes, rates the

probability of ADR according to whether or not the suspected drug is discontinued or reduced in dosage, and by evaluating the effects of such discontinuation or dosage reduction on the subsequent course of the CM. Consideration is given to transient and episodic phenomena, irreversible events, the possible development of drug tolerance, and concomitant specific treatment of the CM in arriving at the rating on this axis.

Axis VI: Rechallenge This final axis weighs the probability of ADR based on what happened to the CM if the suspected drug was either reinstituted or substantially increased in dosage after previous dosage reduction. New clinical conditions are taken into account, as are any treatments that might have been administered to prevent recurrence or exacerbation of the CM.

A scoring system is incorporated into the body of the algorithm. Based on the weight of the evidence on each axis, a score of +1, 0, or −1 is assigned. If the evidence clearly favours the diagnosis of an ADR, a +1 is obtained. If the bulk of the evidence is clearly against the diagnosis of an ADR, −1 is scored. If the evidence is either insufficient, equivocal, or contradictory, a score of 0 is assigned. There are two particularly important logical branch points that are given extra weight. A +2 score may be obtained on Axis II in the absence of any alternative aetiological candidates, and a −2 score is possible on Axis III if the timing of events is inconsistent with an ADR. These extra weights were found to improve validity of the instrument in our preliminary testing.

In order to arrive at an overall probability that the untoward clinical manifestation represents an ADR, the individual scores on the six axes are simply added together to get a total score. With the extra weights possible on Axes II and III, as mentioned above, the range of total scores is from −7 to +7. Based on the total score obtained, a probability category is assigned according to the following ordinal partition: if the total score is +7 or +6, the probability of an ADR is definite; if +5 or +4, an ADR is probable; if +3, +2, +1 or 0, an ADR is possible; if less than 0, an ADR is unlikely. These four ordinal probability categories of definite, probable, possible, and unlikely are the same categories usually mentioned, but as yet unspecified, in the ADR literature.

When a patient is on more than one drug suspected of causing a CM, each possible paired combination of drug and CM should be submitted to the algorithm and scored separately. Thus, when several drugs are being taken, the algorithm can be used to determine which one is the most likely cause of an observed CM. All the drugs receiving lower scores will have their Axis II score automatically revised to −1, since the highest-scoring drug now becomes a good alternative candidate. With minor modifications in wording, the algorithm can also be adapted to assess adverse reactions to drug withdrawal and adverse drug interactions.

By using the algorithm questionnaire to score a series of test cases, Hutchinson *et al.* (1979) have been able to demonstrate the reproducibility and validity of the instrument. By reproducibility, we mean that different observers using the algorithm arrive at the same probability assessments. Validity denotes the ability of the algorithm to yield a score that conforms to the judgment of an expert or a consensus of experts. Leventhal *et al.* (1979) have reported the results of a study in which internists and paediatricians were able to substantially improve the reproducibility of their ADR assessments by using our algorithm questionnaire. Although the procedure does not produce anything approaching unanimity, residual disagreements tend to be minor (usually the difference between 'neighbouring' probability categories), and its use in several settings and by a number of clinicians has resulted in a significant improvement in the consistency and conformity of the assesssments by those clinicians.

The ADR algorithm has a number of potentially useful applications. The main value probably lies in its use as a methodological tool in ADR epidemiology and drug surveillance. In addition to helping to standardize incidence rates, the algorithm could also be incorporated into the early warning system so important in post-marketing surveillance and thus be of potential benefit in monitoring activities by drug manufacturers and regulatory agencies. This may also have important implications for drug policy by aiding decisions made by public health or government officials. The algorithm might be used in ADR monitoring of individual hospitals or physicians, that is, quality of care and peer review. Clinical toxicological investigations of controversial drugs could be accomplished by assembling a series of case reports and scoring them on the algorithm. Kramer *et al.* (1980) have completed such an investigation of adverse effects attributed to gamma benzene hexachloride, a popular scabicide and pediculicide. Finally, the algorithm, despite its seeming complexity, could be of potential value to the individual clinician who wishes to assess the likelihood that an observed untoward clinical manifestation in his or her patient represents an ADR.

Conclusions

There is no question but that ADRs are becoming increasingly important phenomena in the world of clinical therapeutics. We cannot, however, turn back the clock to Hippocrates: mere avoidance of harm is no longer enough. In this day of potent chemical agents, adverse reactions are to some extent ines-

capable. Given a choice between no treatment and effective treatment with a risk of toxicity, the physician must usually select the latter. Our job is to maximize the benefit and minimize the risk, but before we can minimize the risk, we must first be able to assess it accurately. And the need in this accurate assessment of risk is not for more numbers—more registeries, more computers, more reports of ADR incidence in the literature. The need is rather for standardized evaluation—that is, not just more data, but more reliable data. This is a need that will never be met in the laboratory, nor in the legislature, but only by attention to the inescapable difficulties and complexities inherent in trying to assess the adverse effects of drugs.

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