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CURRENT OPINION

Adverse Drug Effects and Their Clinical Management: A Personal View

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Abstract This paper describes the personal views of the author about diagnosis and management of an adverse drug effect. It proposes that diagnosis is complicated and is also supported by carefully observed management of changes in drug therapy. Drug-related adverse effects may be due to the drug itself, though many are due to systematic errors occurring in the process from diagnosis of the primary treated condition, through prescribing and dispensing, to the way the drug is used by the patient. Bringing awareness of such systematic errors for consideration and management is part of a health care professional's responsibilities.

Key Points

Clinical diagnosis of adverse drug reactions and patient management are complex, interwoven processes.

Clinical information and experiences about individual patients will aid prevention of adverse drug reactions.

Provision of adverse drug reaction information must be timely, and relevant to support busy health professionals in their consultations.

1 Introduction

Because of the multiplicity of definitions in the world literature, for clarity the following definitions are used in this article. "The term 'adverse effect' encompasses all unwanted effects (*including test results indicating harm without any obvious clinical symptoms/signs*); it makes no assumptions about mechanism, evokes no ambiguity, and avoids the risk of misclassification" [1]. The term 'adverse drug effect' (ADE) refers to an adverse effect where some attribution to a drug, or to the use or misuse of a drug, has been made. An 'adverse drug reaction' (ADR) is the clinical response of a patient to a drug, defined here as "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the drug regimen, or withdrawal of the product" [1].

Adverse effects and adverse drug reactions constitute major morbidity and sometimes mortality, but how to make a diagnosis and manage adverse drug effects in an individual to avoid or reduce serious harm does not receive much attention.

Accurate diagnosis is essential to good patient management. There is a limited way in which the body may respond pathophysiologically to drugs and other disease assaults. This means that adverse effects often masquerade as other diseases. In some more unusual instances, adverse drug reactions may be more commonly related to drug or chemical exposure than to alternative possible causes (such as agranulocytosis or Stevens–Johnson syndrome), making the diagnostic challenge somewhat easier. It is much more difficult to decide on the diagnosis in an individual when other causal probabilities are more likely than a drug, and when actual evidence that exposure to a particular drug has occurred, in what dose and when, may be difficult to ascertain.

Therapeutic error, unexpected failure of effect (perhaps related to a substandard/counterfeit product), drug abuse,

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accidental or suicidal self-administration, and homicidal use of drugs are all also adverse drug effects, which the wise clinician needs to bear in mind. There is a strengthening view that we have neglected this area of adverse effects related in some way to drug use. They need diagnosis not only in terms of the adverse effects but also why they occurred. We need to examine systematic causes of adverse effects in all individual situations to help find ways to prevent harm in the future.

Avoidable adverse effects of treatment, which are essentially medical errors, form about 70 % of the adverse drug reactions leading to hospital admissions [2]. There are many reasons for medical error, ranging from outright negligence to mistakes made by conscientious health professionals who are too tired or pressured or distracted. The ultimate causes may be multilayered and can only be fully evaluated by tracing back to the ultimate causative factors—this is a long process but may be very important in order to discover system errors, which can be managed, and avoid problems in the future. Simple examples of such an approach might be improved working hours to avoid tiredness and stress, or double-checking the interpretation of prescriptions prior to dispensing, to avoid errors due to misread handwriting.

The root cause(s) of adverse effects may be complex, and investigation is time consuming and so does not form a major part of clinical evaluation. On the other hand, the clinical staff managing a patient are usually in the best position to at least institute an evaluation of the circumstances surrounding a serious adverse effect where some medication error is probable. The ensuing investigation will include causes of systematic problems in health care delivery, and other factors. Understanding of such systematic errors is important to find ways of preventing them, rather than to blame individuals.

It follows that practising clinicians must always consider adverse effects as part of their clinical diagnosis and in the overall context of patient management. It should always be borne in mind that not only do drugs affect diseases—diseases affect drugs (see Sect. 3.3). The causal relationship of a drug to a clinical event may be far from easy to distinguish from other (disease) candidates in the differential diagnosis.

2 Clinical Diagnosis

The contemporary approach to clinical diagnosis is methodical and has been developed over centuries. Broadly, the diagnostic process starts with taking a careful case history, through the standard procedures for physical examination of all of the body's organ systems, to selecting and applying the results of various external tests. The sensitivity and selectivity of both the clinical history description and examination findings, as well as laboratory investigations that lead to diagnoses, are important. Quality considerations of all of the evidence used for diagnosis are paramount.

Currently, the development of evidence-based medicine has emphasized the uses and value of clinical trial and epidemiological data, but such information does not necessarily help with the individual patient at hand, for a number of reasons. This may be particularly true of safety information about drug products.

When all of the evidence is assembled and a differential diagnostic formulation is proposed, there are decisions to be made. Traditionally, clinicians use a heuristic (previous knowledge- and experience-based) approach to diagnosis to give priorities to what is hopefully a comprehensive list of possible diagnoses. The clinical heuristic approach is still the most commonly practised approach anywhere in the world.

The main disadvantages of clinical heuristic judgement are that:

- The probability of the health professional remembering previous experience or knowledge of a similar event is very variable.
- The probability of the health professional being able to link the presenting case information to that experience may be compromised by incomplete or partially discrepant case information.

The performance of clinical diagnosis can be very heterogeneous, particularly for supposedly minor illnesses, when there may be only one patient visit, and when practitioners are generally under time pressure. Increasing fragmentation of medicine into specialties may lead practitioners to focus only on certain areas of clinical interest in the heuristics of their clinical evaluation.

On the other hand, clinical diagnosis often operates in a Bayesian fashion for more serious illnesses. Each part of an often evolving pattern of findings is usually examined critically in an iterative way, with new information being used to create a new prior probability. The process may involve a number of competent health professionals with different experiences, giving a peer review of the diagnostic process. In these circumstances, the probability of a correct diagnosis is high, certainly better than notional 50 %.

Differential diagnosis can be partially or even entirely automated, using predictive algorithms designed and tested for the purpose. These algorithms are increasingly used: the clinical findings in any particular diagnosis can be compared for their probabilities (including the presence or absence of component findings) with known, typical information for any of the possible causes.

In pharmacovigilance, however, one may use other findings as additional support for a causal association. These include a dose–response finding (a high dose causing a known pharmacological effect); a known reasonable temporal relationship in the clinical findings; and de-challenge information. Added to this may be some external knowledge: analogous drug patterns; experimental evidence; and a plausible mechanism. Some adverse reactions are predictable from knowledge of the basic pharmacology of the drug concerned, such as overdose, drug withdrawal syndromes and when there is reduced ability to eliminate the drug—for example, in patients with progressive liver/renal disease. The valuable guidance given by Bradford Hill in assessing such factors in causation includes other pointers that can be taken into account [3, 4].

Diagnosis of an adverse drug effect is inextricably mixed with management of the patient. Changing aspects of the patient's drug therapy is an observable experiment that can critically alter the probability of a drug causation. The value and problems associated with this are discussed below.

3 General Considerations in Clinical Management of Adverse Drug Effects

From the above, even though one may suspect an adverse drug reaction as a diagnosis, it is not easy to determine a causal relationship, unless there is a special investigation result that is specific. This is not usually the case. It is often claimed that diagnosis in individual cases cannot 'prove' causation alone. Aronson and Hauben [5] have argued that it is clearly possible in some cases. It also seems clear that careful clinical management of a patient, with close monitoring of the patient's responses to manipulation of the drug(s) used, as well as exclusion of more likely causes, can lead to a diagnosis with a high probability of drug causation. This is to be contrasted with epidemiological evidence, which demonstrates a probability based on the incidence in an exposed group versus controls. For rare adverse reactions, the lack of power of some observational studies may be insufficient, and controlled clinical trials may be impracticable because of costs. Individual case information remains very valuable, not in quantitative terms, but in showing with high probability that a particular adverse drug effect can indeed happen at least once [6].

3.1 Ensure a Complete Medical History

First, it is necessary to be as sure as possible about drug exposure, to avoid diagnostic errors. Depending on the nature of the clinical situation, a very careful history of drug use is of primary importance. If the clinical finding is likely to have a subacute or chronic cause, the drug history must go back to a time well before the likely onset of the complaint. Care should be taken to determine exactly what drugs were taken and when, as well as asking about the patient's adherence to the drug regimen being used. This raises the issue of the patient's memory of drugs and events. To approach a patient and only ask about drugs taken is very likely to miss some important points. It is often more revealing to ask about illnesses or symptoms the patient may have had and find out if they used drugs to manage them. This approach is likely to pick up the use of self-prescribed products, such as over-the-counter drugs and 'alternative' remedies, and the use of other people's drugs. The patient should be asked specifically about the use of drugs such as oral contraceptives, chronic treatments (always ask about the use of anticoagulants) and also the use of recreational drugs. Illicit drug use information may not be volunteered, and the clinician needs to remain aware of illicit drug use and use careful questioning!

3.2 Specific Tests for Adverse Drug Effects

There are some diagnostic tests that can be used for adverse reactions/effects. Some may be useful in simply looking for suggestive diagnostic patterns amongst standard tests—for instance, liver function, or perhaps specific histology from biopsied lesions.

For some drugs, there is the possibility of specific drug monitoring to assess whether the drug level in blood, plasma or another body fluid is at a therapeutic, and not toxic, level. Such monitoring is available for a variety of drugs with a small difference between therapeutic and toxic levels—a 'low therapeutic index'—and is particularly relevant to pharmacologically related adverse reactions. For allergic/idiosyncratic adverse reactions in patients, fewer confirmatory tests are available, but the number is growing. Skin, blood and urine tests are available to confirm acute and chronic allergic reactions.

3.2.1 Manipulations of Drugs and Doses

A more interventional approach is usually needed. Exposure to a suspected drug may be manipulated by altering the dose or discontinuing the drug(s). Using the timing of the start and discontinuation of treatments in relation to symptoms and signs is a crucial aid to diagnosis, helping to fulfil some of the Bradford Hill proposals mentioned above [3].

Adverse drug reactions are not all that common with individual registered drugs. As mentioned above, there are usually competing disease probabilities for any set of symptoms that may have higher prevalence. The differential diagnosis will then depend upon exclusion. One should

look for causes other than drugs and do investigations that will show known high probability in assessing their presence or absence. If suspicion of drug causation is strong, particularly if the patient's condition is serious, this may include stopping any suspect drug as a necessary management step. This important de-challenge must be observed carefully to see whether, and how, the condition improves or goes away entirely, in a way in keeping with what one expects from that condition and the kinetics of the drug. To do this, one must have a clear idea of how the patient should be reviewed and monitored—for example, by clinical assessment only or by specific investigations [7]. Appropriate information from a successful de-challenge suggests at least a possible causal effect of the drug.

From a clinical management viewpoint, de-challenge must be considered carefully. First, what are the risks of removing the drug? If the drug is essential for the patient's wellbeing, will it be possible to observe any change in a suspected adverse drug effect before one must re-commence the drug, if that is likely to be necessary?

The risk/benefit profiles of suitable alternative therapies should be considered, including the possibility of cross-sensitivity or other shared reactions of drugs in a similar therapeutic group; substitution may be the best option but carries the chance of introducing confusion through cross-activity.

Information on the success or otherwise of changing from one treatment to another is not always easy to assess, since adverse reactions are rare, and the information on the best options for substitution is often to be found scattered in a few case reports on a particular drug and adverse reaction.

Observing the dose response to a drug is always useful in diagnosis. If the drug history suggests that an adverse drug effect occurred after an increase in dose, a dose-related adverse effect is possible, and dose reduction may be a viable alternative to discontinuation. One trap in assessing dose response in the treatment of chronic diseases is where a drug dose has been previously increased to control a deterioration in the disease. It is then possible to confuse whether a new adverse clinical effect may be due to the increased dose of the drug or to some aspect of the worsening disease that is still not controlled by the drug.

Similar thinking may apply if another drug is added to manage a deteriorating patient. In that situation, there is also a need to consider the possibility of a pharmacokinetic or pharmacodynamic interaction as well (including possible additive effects between drugs).

When several drugs are taken together, and particularly if they are changed at the same time, the diagnosis and management are complicated. Knowing the relative incidence of an adverse drug effect related to the suspect drugs will be helpful, but there is only limited help available from the drug literature on the incidence of adverse reactions to different drugs. In practice, the most rational approach is to withdraw the least necessary and most likely drug first. One should certainly suspect the drug(s) that have been changed most recently in the patient's treatment, and use whatever adverse drug effect incidence information is available for the drugs being used. With the most severe reactions, one must stop all likely drugs; with milder reactions, it is possible to simply assess the drugs one by one, using some kind of compound comparison of probability, the severity of the adverse drug effect and the benefit of the drug to the patient.

3.3 Interactions

When the patient is taking more than one drug, interactions must be considered. Some only consider reduced effectiveness of one drug, or a greater-than-additive effect between two drugs, to be an interaction, due to enzyme induction or inhibition, respectively. In clinical practice, one often encounters two or more drugs where their pharmacodynamic effects are additive, causing clinical problems. Inhibition of pharmacodynamic effects has been mentioned (Table 1), where patients on beta-blocking drugs may not respond as well to adrenaline. These are often avoidable medication errors.

Interactions can also occur with food products that can alter cytochrome P450 (CYP) enzyme function. It is also important to remember disease processes that may alter drug clearance, particularly liver and renal function.

3.4 Genotyping

Genetic tests can determine the susceptibility of individuals and include general tests, such as tests for porphyrias and sickle cell anaemia, and specific tests for drug metabolism, such as acetylator status and liver oxidative enzyme status. These tests are also very useful in preventing problems with subsequent drug treatment (see below).

The potential for genomic/proteomic information to be useful in diagnosis and, more importantly, prevention of idiosyncratic adverse reactions to drugs is great but is still in its early phase. A particular challenge is to understand the factors that affect gene expression (including drugs) before genomic data are of great practical value. Another challenge is the cost effectiveness of genetic screening for relatively rare phenotypes. There are, however, some examples of the use of genomic data in predicting safe use of drugs, such as the antiretroviral drug abacavir. Abacavir hypersensitivity reaction is a potentially life-threatening adverse drug reaction, which affects approximately 8 % of patients. It has been shown that there is a strong predictive association between this hypersensitivity reaction and

Table 1 Some common and serious adverse reactions and their treatments

Adverse reaction	Treatment	Possible problems
Anaphylaxis	Adrenaline	Effect reduced if patients are using beta-blockers
		Cardiac arrhythmia
Bleeding from warfarin	Vitamin K	Hypercoagulability and warfarin ineffectiveness
Convulsions	Benzodiazepines first, possibly phenytoin	Phenytoin may induce hepatic enzymes
Arrhythmias	Various drugs, depending on the precise arrhythmia	May cause their own cardiac effects

*HLA-B**5701, indicating that exclusion of *HLA-B**5701-positive individuals from abacavir treatment would largely prevent this reaction.

There is also a test for the susceptibility of patients to develop Stevens–Johnson syndrome and toxic epidermal necrolysis after exposure to carbamazepine. The *HLA-B**1502 antigen for this serious adverse drug reaction is particularly prevalent in the Han Chinese population [8]. This finding was the result of pharmacovigilance activity in Taiwan, which demonstrated a higher than expected rate of Stevens–Johnson syndrome and toxic epidermal necrolysis in Taiwan, and has led to the introduction of preventative genotyping there and in other countries [9].

3.5 Re-Challenge and Desensitization

In spite of the use of the above methods to diagnose adverse reactions, uncertainty over causation can remain. A final test that is very helpful is re-challenge with the drug(s). Ethically, re-challenge may often not be justified; clearly, the severity of the reaction that may re-occur versus the need to be certain about the reaction and the availability of suitable alternative drugs are major considerations: deliberate re-challenge remains a difficult management matter. Re-challenge may, for example, sometimes be justified when life-saving drugs, such as anaesthetics or antibiotics, are likely to be needed by a patient in the future. Always, a full explanation of the benefits and risks of the procedure should be given to obtain fully informed consent, and full resuscitation equipment must be immediately available in the event of anaphylaxis.

Re-challenge should only be undertaken when the patient has recovered completely from the first reaction. Re-challenge means that precisely the same drug, in the same formulation, at the same dose, is given to the patient again, for as long as is reasonable to reproduce the adverse effect. The aim is to see if the same effect is produced under controlled conditions simulating, as far as clinically reasonable, the first exposure.

It is important to differentiate re-challenge from re-exposure. Re-exposure is an accidental event in which any of the above specific re-challenge requirements is in doubt. For example, a patient who has a rash following treatment with amoxycillin and gives a history of a rash following penicillin 30 years before is not to be described as having a positive re-challenge, even though the reaction is likely to be cross-sensitivity.

The use of desensitization programmes in the case of drug allergies is a related difficult management matter because of the risk of life-threatening reactions, and also needs fully informed consent from the patient. The use of a penicillin or other skin test or desensitization for allergy should not be considered a re-challenge in pharmacovigilance terms. This is because the dose and route do not mimic the way in which the drug was used initially. Note that this does not mean that such tests do not have a place in diagnosis and treatment, but their place is limited.

Many ‘re-challenges’ occur accidentally and do not fulfil the full criteria mentioned above, and are therefore to be regarded as accidental re-exposures.

3.6 Treatment of Adverse Drug Effects

It is clear from the above that the management of adverse reactions is linked with the diagnostic work-up, since the major step is to stop the likely responsible drug or to reduce the dose. Either because the drug is deemed essential or the effect is very severe, this obvious solution is not always sufficient, and patients may need or request additional active treatment.

When treating an adverse drug reaction, there are two useful guidelines:

- Do not confuse the clinical picture unnecessarily by using more drugs unless absolutely necessary!
- Have a clear objective for the treatment, carefully monitoring its success or failure, with a general aim of not using the treatment for longer than is necessary.

The treatment situations are threefold. Firstly, the patient may want treatment during a protracted diagnostic phase. This is difficult, since the new treatment might well interfere with the diagnostic process, but short-term symptomatic treatment—for instance, for pruritus—is acceptable. The use of other drugs for the treatment of a life-threatening adverse effect is naturally essential, but the

choice of drugs must take into account potential interactions with existing drugs. In either case, the new treatment drugs should be discontinued as soon as possible.

Some common and serious adverse reactions and their treatments are listed in Table 1.

Secondly, an adverse effect will sometimes produce long-term and even permanent conditions that need treatment. Examples are pulmonary fibrosis, which will usually need corticosteroid and even immunosuppressive therapy, and acute renal and hepatic failure, which may well need supportive therapy and intensive care and even transplant surgery where that is available. Other surgery may sometimes be necessary for sclerotic adverse reactions affecting the skin, lungs or heart.

Thirdly, and even more unusually, it might be necessary to use a second drug to prevent an adverse effect of a primary treatment drug. This drug may be essential in the patient's treatment by a second drug. For examples, the anti-cancer drug cyclophosphamide causes cystitis, and mesna is nearly always given to relieve or avoid this common reaction; giving potassium supplements to patients using diuretics chronically is general clinical practice to prevent hypokalemia. More controversial is the use of two drugs to treat the same condition, both of them in lower than recommended doses for effective treatment, in order to avoid adverse drug effects. It should be emphasized that such an approach should be considered very carefully, and an alternative using a single drug may be preferable; however, the use of the so-called poly-pill or multi-pill is an interesting innovation [10].

4 Prevention and Avoidable Medication Errors

The following are common causes of adverse drug effects in chronological order from the time of first seeing the patient:

- Failure to ascertain aspects of the medical history and clinical picture that will lead to adverse drug effects (e.g. failure to ascertain previous hypersensitivity to the prescribed drug or a cross-reacting drug, failure to consider genetic predispositions, or failure to consider concomitant diseases, such as liver and kidney insufficiency or porphyrias).
- A wrong diagnosis (and therefore wrong treatment!).
- Failure to appreciate important aspects of the pharmacology of the drug, such as its potential for interaction with other drugs (e.g. warfarin with several drugs) or foods (possibly grapefruit juice with drugs metabolized by CYP enzymes and tyramine with monoamine oxidase inhibitors), and also the changes in sensitivity to some drugs with age.
- Wrong prescription (either an error in decision making or in the writing of the prescription, which might include the dose or dosage frequency, as well as which drug is chosen).
- Wrong dispensing (misinterpretation of the written prescription, or a practical error, or mislabelling).
- Mistakes in drug administration.
- Failures of patient compliance, due to misunderstanding of or failure/inability to read instructions, misperceptions about drugs, bad taste or even appearance of drug formulation, competing advice (e.g. from friends) or suicide attempts, as well as some bizarre problems such as suicide pacts and homicide attempts.

Most of these medical errors are regarded as non-systematic problems—in other words, although the individual situation might have been avoided by some other more appropriate action, there is no *general* avoidance advice that can be given. This is not always true: consider the possibility of mistakes in dispensing due to bad handwriting, confusions from look-alike and sound-alike names, or failure to use the latest product information. For the first example, there is some general advice that may be given: write clearly and in upper case. This is advice that should be given and followed at local health care facilities, but unambiguous naming and clarity in general identification of products is the responsibility of regulators and the pharmaceutical industry. On the other hand, they cannot be expected to anticipate all such problems, and they need to ask for reports of where this has happened. It is an important clinical management function to consider the root causes of medication error, and it should be part of a clinician's role to alert the appropriate authorities to a possible systematic error. Root cause analysis can be sometimes difficult and time consuming, and this may not be the job for a primary health care professional alone, but raising the warning flag is!

The author was involved in such a situation. He was alerted by an anaesthetist that some clear glass ampoules containing different drugs used in the operating theatre were a very similar size and colour, and had only small writing on the container showing the contents, and that the writing was the same colour as well: an obvious risk situation. Although one can argue that a competent anaesthetist should be aware of this, not every anaesthetist is experienced, has perfect eyesight or cannot be caught out in an emergency. The author wrote a report referring to this problem, and notified both the national regulatory agency and the manufacturers. This resulted in a letter to all doctors, drawing attention to the hazard, and later to better identification of the ampoule [11].

The reasonable and effective search for ever-cheaper drug products to keep the economics of heath care under

control does bring other patient safety problems in management [12]. There is evidence about the occasional problems seen with approved generic substitution: in confusion by patients as they see their familiar products replaced by those that look different; where the instructions between products may not be identical; where the size of a tablet may make it difficult to swallow; where a different excipient may cause allergy; and where some medical conditions seem to be susceptible to generic substitution, and one needs to be aware of these [12].

A growing challenge to diagnosis and management of adverse drug effects is the increasing danger from substandard, spurious, falsified, falsely labelled, counterfeit drugs (SSFFCs!). This group of products can be the cause of both unexpected failure of effects and unexpected adverse drug effects. One can only speculate that generic substitution might be one factor in letting SSFFCs into the health care market, but it cannot help when both professionals and patients are faced with unfamiliar drug products very frequently.

Whilst decision support intuitively seems important, a word of caution is needed. One rigorous review of clinical decision algorithms—assessing only 65, where randomized controlled trials were available—found very limited and variable support for improvement in clinical outcomes, whether or not the supports were incorporated into electronic medical record systems [13]. More than that, there were no real pointers as to why that should be so in spite of better than about a 70 % satisfaction rate in the eight studies where this factor was assessed. About 2 % of users also commented negatively about technical issues related to decision support. More telling perhaps, 42 % improved clinical outcomes outside academic settings versus only 6 % within academia were reported. Though the finding was not significant on multivariate analysis, perhaps this could indicate much better possible value to busy general clinicians and their patients.

5 Conclusion

The combination of successful diagnosis and management of a single patient with a suspected adverse drug effect underlies a satisfactory outcome for the patient. It can also produce information that raises a possible signal of potential harm, even to the extent of suggesting a strong possibility (better than a notional 50 %) that a particular adverse drug effect *can* occur in patients, though giving no indication of incidence. Moreover, by delving into the information that was used in making the diagnosis and particularly reviewing the overall characteristics of the patient, many risk factors can be found that might be useful in prevention of further adverse drug effects.

It seems likely that the more information we have in genomics and proteomics, as well as more detailed clinical and ancillary information from health care records, the better will be our understanding of drug risks and their preventability—but only if careful diagnosis and management of adverse drug effects is practised.

Good clinical diagnosis and management takes time, which must be made available for efficient, safe medical practice to be possible. There is potential for much better information technology (IT) support systems for clinical decisions in the future to allow doctors to optimize their time for clinical contact. The development of such resources seems essential if doctors are to provide effective and humane clinical management in the face of the information explosion and, in many situations, their increasing load of non-clinical duties. In 1999, I wrote the following:

"A more distant vision

Doctors, using a computer-aided diagnostic system, would have all known or suspected drug and chemical causes for a particular symptom or diagnosis brought to their attention.

These would have information on frequency and likelihood of causality. They would be able to get more detailed information on diagnostic criteria in a drop down menu. They would also be able to try the patient's history and physical findings in a diagnostic model and get a probabilistic decision tree to aid their diagnosing. Suggestions for further evaluation and investigation would also be made.

Once the diagnosis has been decided, management/therapy options would be available from the software. Benefit and risk information for these would be presented, including a no-treatment option. Certainty and doubt would be shown and contraindications, warnings and interactions mentioned.

The act of prescribing would bring to the prescribers' attention any incompatibilities based on medical and drug history, concurrent disease and other drug, dietary, occupational/hobby chemical factors etc. recorded for this particular patient.

The act of prescribing would also enter the details into a central database, where anonymised data will be stored and mined for relationships. The patient would have his/her own data updated on his/her own smart-card.

Any further medical attendances by the patient would result in any new clinical event being linked to, amongst other factors, a drug. This drug/event relationship could possibly exceed a warning threshold in the central database (via machine learning).

Then the next prescriber using the network will get to know this, if the information is relevant to his/her patient: so will the people whose responsibility it will be to investigate the potential signal further. So will the patient have this possible new ADR on his/her smart-card" [14].

We may be getting closer to this still futuristic vision, and perhaps the current mixed results of IT-based decision support systems on outcomes will improve as they improve. It may also be that decision support for changing information on adverse drug effects that will be less familiar to physicians may be more useful to them.

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