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Clinical Diagnosis
A Topic Worth Revisiting for Pharmacovigilance

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There are now 7 million reports in the Uppsala Monitoring Centre (UMC) database (Vigibase™) held in trust for the WHO Programme for International Drug Monitoring.[1] Each of these individual case harm reports (ICHRs) represents a suspicion by the reporter that a drug may have been responsible for a harmful clinical effect. The Reverend Donald Messer gives a poignant view on statistics such as these, in a sermon about AIDS:

''As an African proverb proclaims, 'Statistics are numbers without tears.' We simply fail to identify with numbers; they are nonpersons in our minds and hearts. Facts without faces do not evoke within us a sense of personal compassion or religious commitment. As the poet and essayist, Archibald MacLeish, once suggested 'We are deluged with facts, but we have lost, or are losing, our human ability to feel them'.''[2]

Apart from this humanitarian imperative, it is important for us to recognize that each of these reports represents a clinical diagnosis and causal statement, or at least an inference, by the reporter.

1. What is a Clinical Diagnosis?

The approach to clinical diagnosis is methodical and has been developed over centuries. The content of Macleod's text book *Clinical Examination* is a good example of the systematic approach to this clinical art – the book having evolved slowly over many years since its introduction in 1964. Such texts describe processes that lead from taking a careful case history, through the standard procedures for physical examination of all the body's organ systems, to selecting and applying the results of various external tests. Modern medical texts such as Davidson's *Principles and Practice of Medicine* also have introductions to the issues of sensitivity and selectivity of laboratory investigations in diagnoses as well as outlining the challenges posed by the heuristic (previous knowledge- and experience-based) approach to diagnosis. The uses and value of clinical trial and epidemiological data is emphasised but, as always, the latter information does not necessarily help with the patient at hand.

In the past, even before the advent of computer- and investigation-aided diagnosis, there has been a limited application of clinical algorithms that implied qualitative considerations of specificity and selectivity. For example, the diagnosis of rheumatic fever was made using an algorithm devised by T. Duckett Jones in 1944, and which has been updated periodically since.[3] The algorithm is simple and describes 'major' and 'minor' diagnostic criteria, the former being more specific than the latter. Nevertheless, the clinical heuristic approach is still the most commonly practised anywhere in the world.

The main factors affecting clinical heuristic judgement are:

- The probability of the health professional remembering previous experience or knowledge of a similar event: memory is very variable.
- The probability of the health professional to be able to link the presenting case information to that experience: the clinical patterns in both the background and the case may be incomplete or vary in some respects.

- The prior probability is often set by the above thinking based on the patient's history and perhaps physical impressions, followed by collection of more historical information, more detailed examination, and various investigations. Each step results in a posterior diagnostic probability that sets a new prior probability for further investigation, and so on: the prior probability of the clinical impression crucially sets the scene. It may also be that if one diagnosis appears obvious early in the process, the full diagnostic procedure is curtailed because of time constraints or is given a direction which is spurious. For example, a blood culture or a drug level result may be available early, and will have considerable influence on a patient's further evaluation because of the high specificity to a possible causal agent.
- It will be clear from the above that a very self-critical and open-minded approach to the early appraisal of the patient will lead to the best results!

So, clinical diagnosis is very heterogeneous in its performance, particularly for minor illnesses, when there may be only one patient visit, and when practitioners are generally under time pressure. Another factor is the increasing fragmentation of medicine into specialties that may lead practitioners to focus only on certain areas of clinical interest in the heuristics of their clinical evaluation. Details of the clinical presentation *can* be fully ascertained in the individual, although aspects may be missed during the assessment of the patient or may be yet to be found as the patients disease evolves.

It might seem that there is very little on which to build any confidence on a clinical diagnosis in determining causation, but this would be to ignore the value of an essentially Bayesian nature of diagnosis. Each part of an, often evolving, pattern of findings, is usually examined critically in an iterative way, and probably by a number of competent health professionals. Every diagnosis is inferential, depending upon multiple observations and premises. Every factor considered in a diagnosis, including time relationships and more, has a causal strength, both positive and negative. The diagnostic pattern of clinical findings in a patient is generally compared with known patterns that are related to each possible cause – a process and argument which is called 'differential diagnosis' as outlined above; in other words, 'what are the strengths and weaknesses of proposed alternative diagnoses.' It is the coherence of the total pattern and the elimination of possibilities, as well as accumulation of supporting evidence, that is the strength of a diagnosis to a critical professional.

Differential diagnosis can be partially or even entirely automated, using predictive algorithms designed and tested for purpose. The probability that a clinical finding or condition would have occurred in the first place in an individual based on previous knowledge and experience, however obtained, is not necessarily the same as the probability that the presentation or condition *has* occurred in any particular individual patient. If the contributory probability fractions of each component of the clinical presentation to the total diagnosis are assumed to be the same, relatively, then:

- The probability of any clinical finding to have been caused by any candidate diagnosis is proportional to the probability of the diagnosis, and, secondly, depends on the rate at which the diagnosis causes that particular finding.
- The prior probability that a diagnosis would have occurred in the first place in an individual is approximately equal to that of a population that is as similar to the individual as possible except for the current findings, but also considering, where possible, any relative risks given by known risk factors that distinguish the individual from the population. (A possible variation is that there is no abnormality, and only a relatively unlikely variant of a normal state.)
- The product of the probabilities for each clinical finding gives the total diagnostic probability.

This diagnostic approach allows the differential diagnoses to be compared by the probabilities (including the presence or absence of component findings). The clinical findings in any particular diagnosis can be compared with known,

typical information for any of the possible causes. Such an approach also allows the consistency of a diagnosis in case series to be evaluated, and it allows the overall probabilities of diagnostic patterns to be compared to each other if the suspected causes are included as part of the pattern.

In practice, all clinical diagnoses depend upon eliciting as many of the component findings to form a pattern as is judged necessary by the clinician. The number of findings used in the diagnosis may therefore be very variable, but the more factors that are included and evaluated in the different patterns of candidate diagnoses, the more likely it is that the comparisons will be useful in differentiating between diagnoses. Useful variables may not be recorded, such as the evolution of the patterns in a diagnosis and the chronology between the various findings. This kind of information has been particularly useful in the diagnosis of infectious disease in the past and is very useful in pharmacovigilance too. In respect of complete chronological information, the current requirements for reporting clinical findings in ICHRs is not good, unless the reporter makes satisfactory use of the free text area.

In considering whether a diagnostic pattern of findings has a causal relationship to a drug in a single case, the main strength lies in the logical coherence of the components of the pattern and any other external evidence. In pharmacovigilance, however, one may also consider as part of the diagnostic pattern, as additional support for a causal association, a dose-response finding (high dose and known pharmacological effect), and a known reasonable temporal relationship within the pattern. To this might be added some external knowledge: analogous drug patterns, experimental evidence and a plausible mechanism. The guidance in assessing causality given by Bradford Hill includes other factors that can be taken into account.[4] In even a small series of cases describing possible adverse effects of drugs, consistency may play an important part in suggesting a possible causal role, and it may be that some findings will suggest an exclusive or rare trait in the diagnostic pattern, indicating a specific risk factor. Exclusive findings not only serve to clearly differentiate between possible drug causation and other causes, but also suggest particularly susceptible individuals in whom exposure to the drug should be avoided if possible.

Many diagnoses of adverse drug effects are made by exclusion. Often this is based on asking for additional findings (such as special tests) that may help to negate other possible diagnoses. As with all the other findings, it is important to know the predictive values of the additional information, and to see it in context.

2. Relevance to Pharmacovigilance and Patient Safety

ICHRs are often described as 'anecdotal', defined in the Oxford English Dictionary as ''A short amusing or interesting story about a real incident or person''. Such a description effectively trivializes and undermines the care and knowledge that is behind the clinical diagnosis, which is in turn reported by an ICHR. What is more important to recognize is that the extent of the work and the knowledge that is behind a clinical diagnosis is not represented in reporting forms, whether they are International Conference on Harmonisation E2B-based or any other format I know. Even a basic question such as, 'what is the strength of evidence supporting this diagnosis', or, 'what other diagnoses were considered and excluded', would help reviewers to judge the evidence for a drug causing the reported effect. It should be possible to design better ways of reporting and analysing more extensive information using Internet and mobile phone applications. Modern informatics must replace old paper-based approaches to do justice to the key information supporting a diagnosis, and that we need.

For patient safety, a reliable diagnosis is essential for the right treatment selection. In this context a 'reliable diagnosis' does not only include the illness that is the target for the proposed treatment, but also any concurrent illness or other factor that might influence the choice of treatment. Although best avoided, a 'therapeutic trial' in a patient is sometimes justified, perhaps in clinical settings where there are few diagnostic tests available. In any case, diagnostic use of a therapeutic agent sometimes occurs by chance,

during the use of a specific-enough treatment that allows a diagnosis based on the success or failure of that treatment. Such information is useful and should be part of a patient's clinical follow-up assessment, a topic I dealt with in a previous editorial.[5]

In pharmacoepidemiology there is relatively little discussion of the strengths of the clinical diagnoses of subjects in studies, and this is particularly true of studies nested in longitudinal healthcare record cohorts. I hope that from the above discussion it is accepted that a diagnosis has varying degrees of probability, not least determined by the evidence used to include and exclude other possibilities. Inclusion and exclusion criteria may well be quoted, but what probability do they have for the diagnosis in question?

3. Conclusions

We know that 7 million ICHRs is just the tip of the iceberg of patients who are variously damaged by drugs.

There is almost no effort to turn our ICHR 'anecdote' reporting into better ways of collecting more useful information, which would lead to better and more sensitive analysis; we continue as we are in spite of ongoing complaints of underreporting and of poor quality data in ICHRs.

Robust diagnoses are at the heart of pharmacovigilance and patient safety. We need to use much more sophisticated informatics approaches to get us the diagnostic information we need to be able to assess possible adverse drug effects properly. We need the details of patients' experiences as well as numbers.

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