

Evaluating Drugs from Cradle to Grave—Evolving Systems for a Complex Activity

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“The desire to take medicine is perhaps the greatest feature which distinguishes man from animals”

William Osler (1849-1919)

Are medicines dangerous chemicals or life enhancing agents? The answer is ‘Both of those things, often at the same time, and worse in the wrong hands’. In this issue of the Annals, several authors address the problems besetting specialists who assess drug efficacy and safety. The last two articles describe activities (pharmacogenetics, and engineered drug delivery) which may produce unforeseen problems for drug evaluation.

Some factors permeate the history of drug evaluation by physicians, scientists and government regulatory agencies. The first is the hypothetico-deductive method in measuring drug action. Most medicines were not truly effective before the highly selective drugs of the modern drug era, and there were few standards governing quality, safety, or efficacy. Only a drug-contamination mass poisoning in the 1920s provoked extensive quality and safety tests before the first administration to humans, and led to the US Food and Drugs Administration. The second feature is the unpredictability of some serious adverse effects. Systematic tests for drug toxicity merged only after the thalidomide catastrophe of the early 1960s. The third factor is proving drug efficacy in both animals and humans, to high scientific standards. Proof of principle in animal models cannot replace drug testing in humans. The need for rigorous proof produced elaborate guidelines and standards of investigation, e.g. the International Committee on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Use in Humans (ICH) Guidelines.

Efficacy Assessment

For 25 to 30 years, the emphasis in clinical drug evaluation has been to show efficacy in disease treatment or prevention. Because most drugs produce effects rarely greater than 60% (and usually 20%–50%) above base-line measurement, it remains important to evaluate efficacy against inactive placebo, or no treatment at all. The effect of placebo can be as high as 45% from base-line with treatments for pain, mental distress, and many symptoms mediated through the autonomic nervous system or some other neuro-psycho-humoral mechanism.¹ Because many new drugs are minor variants of older molecules, comparative studies against the nearest competitor drug are often sensible, apart from placebo-controlled ones. However, since industry funds much research, objective and sufficiently powered comparative studies are few.

Interpreting Estimates of Drug Effects

The need to reduce the inexactness of outcome measures led to the randomised controlled trial (RCT), now 50 years old. The RCT produces an average value of a measured outcome. The mega-trial evolved later to test a given hypothesis with greater detection power and precision. However, both types of trial mostly detect associations and expected events only.² They rarely establish cause-and-effect linkages; they are usually underpowered to detect unexpected events. A randomised controlled drug trial, conducted properly to measure a well-framed outcome, can yield a reliable result valid in the study subjects, but not necessarily in other populations. Factors that enhance reliability are a large

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drug effect, secure subject randomisation, few crossovers between treatment and control groups, and biologically sound outcomes rather than surrogates. Unfortunately, the opposites occur in too many drug studies, leading to dispersed outcomes, and decreased value. Bad control of study conditions is the bane of multi-centre trials.³ To overcome these problems with RCTs, meta-analysis tries to increase precision and statistical power by selectively combining the results of several independent trials. By combining all possible data, both published and unpublished, the meta-analyst believes the result represents the best available evidence. Despite the advantage of meta-analysis over a poorly designed or conducted RCT, both techniques provide an *average estimate* or summary statistic of a drug's effect. Considerable scientific experience is needed to interpret the estimate properly.⁴ There is no easy way to apply the estimate to individual patients.

Questions of Morality

Investigators also face ethical difficulties in efficacy studies. In assessing drugs, some physicians conduct RCTs that generate important ethical debate. Why does this matter to pragmatic Singaporeans? Because drugs are within a global social scheme, and because actions must have a moral basis. In this issue a philosopher explains some trials that appear to contravene fundamental moral principles.⁵ How do we convey enough information to achieve real understanding in the participants? The important forces in this debate affect many lives, and they are not new. Exploitation of ignorance to one person is a business opportunity to another. History will judge the evaluation of anti-HIV drugs in terms of justice, the autonomy of individuals, and beneficence (non-maleficence). Whereas for many investigators non-maleficence wears the Utilitarian cloak, non-maleficence carries a different meaning for most people. Some people in Uganda took part in trials which they could not fully understand. If we accept the Utilitarian concept, that a few persons may usually be exploited for the sake of the many, then civilisation has unravelled a bit more.

Cognitive Challenges

The New Economy is with us. Our nation is developing support for transnational pharmaceutical companies vying for the markets for drugs treating common human diseases. There is pressure to market drugs as early as possible to maximise profit. In assessing the total evidence for a drug, the physician or scientist makes a decision about harm or benefit from time-limited studies.⁶ For instance, the Food and Drugs Administration (USA) had to extend some drugs' patent lives by six months in exchange for company-sponsored studies in children. So, physicians must decide, on incomplete evidence, whether likely benefit exceeds likely harm before prescribing a drug. This is a great responsibility. We need a serious upgrading of cognitive skills, just for prescription-drugs. The trend towards indiscriminate consumption of 'health boosters' is not matched by careful studies of either efficacy or safety of many substances that are classified *by default* as foods.

There are only a few clinical pharmacologists in Singapore. We need more of them to teach rational drug usage and clinical pharmacology, to train clinical drug investigators, to work in the Centre for Drug Evaluation of the Ministry of Health, and to support the specialists who conduct drug trials. All physicians need to contribute actively to pharmacovigilance. The growing pharmaceutical industry in Singapore demands a matching responsibility in our health professions. Will our society rise to these great challenges?

Striking the Best Balance for the Future

The drug evaluator in a government agency employs a familiar strategy to manage the risks of harm to patients. For example, the evaluator has to bear in mind the likelihood of harm to special groups (e.g. children, pregnant women, and the elderly) exposed to a given drug, in contrast to the likelihood of clinical benefit. The action flowing from a judgement of net harm is to restrict the access of physicians and patients to the drug in question. However, restricting access also deprives some people of the drug's potential benefit—and incidentally decreases revenue to its manufacturer. The exercise of judgement is thus open to non-medical influences. It is only too easy to justify difficult decisions using the Utilitarian argument. The next decade will test the integrity of the drug evaluation system in Singapore at all levels, from the investigator, institutional review boards, to the drug evaluator, and beyond. All health professionals and educators must work together to ensure a judicious and equitable outcome.

REFERENCES

1. Oh V M S. The placebo effect: can we use it better? *BMJ* 1994; 309: 69-70.
2. Saw S M, Lim S G. Clinical drug trials: practical problems of Phase III. *Ann Acad Med Singapore* 2000; 29:598-605.
3. Heng D. Megatrials of drug treatments: strengths and limitations. *Ann Acad Med Singapore* 2000; 29:606-9.
4. Chan E S Y. Meta-analyses of clinical drug trials—gold standard reviews or statistical alchemy?. *Ann Acad Med Singapore* 2000; 29:610-5.
5. Williams J. The ethics of placebo-controlled trials in developing countries to prevent mother-to-child transmission of HIV. *Ann Acad Med Singapore* 2000; 29:557-62.
6. Ng T L. Clinical drug evaluation: the regulatory perspectives. *Ann Acad Med Singapore* 2000; 29:616-20.

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