

## For More Reliable and Relevant Research on Treatments

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Imogen Evans, Hazel Thornton and Iain Chalmers. *Testing Treatments: Better Research for Better Healthcare*. The British Library, 2006. pp.113.

Even as this writer sat down to write this review, he came across a study published in *PloS Medicine* which concluded<sup>1</sup> that the type of sponsorship available for randomized controlled trials of statins was strongly linked to the results and conclusions of those studies, even when other factors were taken into account. "...There are many possible reasons why this might be. Some people have suggested that drug companies may deliberately choose lower dosages for the comparison drug when they carry out "head-to-head" trials; this tactic is likely to result in the company's product doing better in the trial. Others have suggested that trials which produce unfavorable results are not published, or that unfavorable outcomes are suppressed. Whatever the reasons for these findings, the implications are important, and suggest that the evidence base relating to statins may be substantially biased."<sup>2</sup>

The book under review is further evidence of this kind: it shows the troubling sloppiness in contemporary medical research and treatment. It is therefore a book very useful for our health. While what the book says may not be applicable for the entire universe of clinical trials in modern medicine, even if 10 percent of the trials were unfair and biased, it has frightful consequences for the public at large.

### Untested Advice

While the authors' try to keep down the shock factor, what emerges is indeed shocking. The case studies and evidence cited for the practice of this unscientific medicine seems to be across academia, medical profession and the pharma industry. Over-reliance on untested theory from experts coupled with biased studies (called "unfair studies" by the authors) has led to avoidable illness and premature deaths. Patients' feedback on unexpected effects of treatments have been routinely ignored.

Dr Spock in the 1956 edition of his famous book *Baby and Childcare* advised to place infants to sleep on the front - an advice that led to the steep rise of SIDS (Sudden Infant Death Syndrome) during the 1970s and 1980s, although not all deaths could be attributed to his advice. Dr Spock's advice, never rigorously evaluated was the result of untested theory - reversing the advice with "back to sleep" led to a dramatic decline in infant deaths

Sometimes what is logical does not work especially if it is based on untested theory: antiarrhythmics - drugs that suppress abnormal heart beat rhythms - do not appear to reduce the risk of premature death after a heart attack, if one

were to extrapolate from the drug's behaviour before the onset of an attack. In fact the opposite seems to be the case: after a heart attack, using antiarrhythmics on patients having abnormal heart rhythms increases the chances of early death. The authors point out that at "the peak of their use in the late 1980s, one estimate is that they caused tens of thousands of premature deaths in the USA alone. They were killing more Americans every year than had been killed in action during the whole of Vietnam War. It emerged that for commercial reasons, the results of some trials suggesting that the drugs were lethal had never been reported."<sup>3</sup>

There are fashionable in vogue treatments like HRT where more and more beneficial effects were/are claimed based on little evidence: HRT was/is apart from being of some use in osteoporosis was/is touted to be useful in prevention of heart attacks and strokes. Current evidence shows that HRT increases the risk of stroke and of developing breast cancer.

### More is not Better

More is not better; and looking for disease in apparently healthy people, as is done in mass screening, can do more harm than good, the authors point out. Harmful effects of mass screening have not been sufficiently emphasized especially with its chances of not detecting all or most who have the disease (not sensitive enough), and the risk of attributing the disease to those who do not have it (not specific enough). The latter as much as the former, once identified as having the disease, are sent into a tizzy of treatments, tested and untested. Examples discussed by the authors are: doubtful mass screening for neuroblastoma (a rare malignant tumour affecting especially young children), screening older men for prostate cancer, screening newborn babies for cystic fibrosis, and dental screening leading to removal of impacted wisdom teeth.

For decades, doctors have been uncertain how much of the breast needs to be removed in case of breast cancer: should one go for total/extended radical mastectomy or selective lumpectomy followed by radiation therapy? Which one has the greater risk of early death? Despite studies showing that there is little difference in outcomes, mutilating surgery continues to be preferred by some as contrasted to breast conserving therapy. "Although there has been much research into breast cancer diagnosis and therapy over the years, the wide variations in the interpretation of screening mammograms and in the use of surgery, radiotherapy and chemotherapy indicate that many uncertainties remain. There are numerous unanswered questions about the basic biological features of the disease such as the role of genes, enzymes, or differences in patients' metabolism. The best treatment of very early stage breast cancers and 'pre-breast cancers' is unresolved, as is the ideal number of lymph nodes to remove from the

ampit. Optimum organisation of screening and treatment services remains contentious, and so requires more evidence to inform practice.” (p.52)

In cancer especially, there is need for randomized trials comparing less drastic treatment with more drastic treatment.

The point at issue is medicine, if attention is not paid to biases and chance, tends to be even more of an uncertain science. Our knowledge as Popper points out is finite and ignorance infinite. Biased under-reporting seems to occur rather too frequently for user comfort. Dramatic effects of treatments, like penicillin, are rare even as they are easily recognizable. Moderate treatment effects are usual and not so obvious

Practitioners are seldom clear on treatment and interpretations. Years ago tonsillectomy was all too frequently done on children irrespective of whether a surgery was really indicated. In the US, tonsillectomy rates and hysterectomy rates as well as percentage of men who had undergone prostate surgery varied drastically from community to community within a State – 15 to 60 percent for prostate surgery and 20 to 70 percent in case of hysterectomy.<sup>4</sup>

The authors also are critical of medical ethicists and ethics research committees not doing their job properly. “Strange as it may seem,” aver the authors, “medical ethicists and research ethics committees have helped to sustain the double standard on consent when there is uncertainty about the effects of treatments. Ethicists often seem more concerned with protecting ‘the vulnerable’ than with encouraging the proper contribution of patients through equal partnerships.”

In fact patient involvement in research is a recurring theme throughout this book. The authors continuously point out how research that does not consult patients at the design stage can often be poor research. That research needs to be relevant is indeed a given. But even relevant research can be done poorly by ignoring patient needs. Activists and patients of breast cancer and AIDS have over the years succeeded in influencing the course of research by demanding that attention be paid to patients’ preferred outcomes.

The book ends with a “blueprint for a revolution” calling for transparency on the part of researchers and practitioners when there are uncertainties about effects of treatments. The same amount of stringency should apply to research on comparing treatments as contrasted to clinical trials of new drugs. Industry should be required to provide better, more complete, and more relevant evidence about the effects of treatment.

In all this is a very useful book for clinicians as well as laypersons on the pitfalls in research on drugs and new treatments; the importance of fair research and how easily lack of vigilance can let unfair, biased and sloppy research and policy making become the norm.

Within India, the importance of such attention to treatment

and clinical research and health policy making cannot be overstressed. The kind of subterfuge in polio vaccination that has gone in India - underplaying or suppressing inconvenient data like vaccine-associated paralytic poliomyelitis (VAPP), jumping to unwarranted conclusions, repeatedly changing the definition of what is a polio case - is bad and dishonest science apart from willfully ignoring hard evidence.

Another instance is that of nimesulide: it does not get banned despite all studies abroad indicating life-threatening adverse events with the use of nimesulide such as hepatotoxicity, renal toxicity, severe skin reactions including fixed eruptions, gastrointestinal toxicity, potentiation of seizures, potentiation of colitis in passive cigarette smoking. In a court case on the issue, the Drug Controller General of India (DCGI) even quoted in defence a “study” done by the Delhi branch of the Indian Medical Association. The “study” in question was a peculiarly Indian twist to evidence-based medicine: an “opinion poll” among just 50 doctors of the over 400,000 doctors in India. The Indian Medical Association (IMA), Delhi branch, came to the conclusion that nimesulide was “safe and effective for all age groups starting with day one to over 60 years” for a variety of conditions, including fever. Later after several twists and turns, round May 2003, the Drugs Controller General of India (DCGI) directed nimesulide manufacturers to withdraw the paediatric “drops” formulation from the market not before IAP (the Indian Academy of Paediatrics) vouchsafed to its “safety”.

On the other hand, the DCGI during 2004-05 promptly banned the Cox-2 inhibitors, Rofecoxib and Valdecoxib, on the basis of its withdrawal by Merck - which raises the question as to what is the modus vivendi of banning/retaining a drug: its international practice or local adverse effects? If it is the former, nimesulide has not been licensed for public use in its originator countries. But it continues to be used in India, thanks to dubious opinion polls and a reluctant regulatory authority. Whereas Coxibs were banned with little or no push from anybody in India using their withdrawal in USA as a precedence. And then several other harmful drugs like analgin continue to exist even though they have been withdrawn from the first world countries.

Reporting bias and underplaying of risk - things that this book warns of - at its worst display.

#### Endnotes

<sup>1</sup>Bero L, Oostvogel F, Bacchetti P, Lee K (2007) Factors Associated with Findings of Published Trials of Drug-Drug Comparisons: Why Some Statins Appear More Efficacious than Others. *PLoS Med* 4(6): e184 [doi:10.1371/journal.pmed.0040184](https://doi.org/10.1371/journal.pmed.0040184)

<sup>2</sup> Quoted from the Editors’ Summary, op.cit.

<sup>3</sup> Authors quoting references on p.8 of the book.

<sup>4</sup> Gigerenzer G. *Reckoning with risk: learning to live with uncertainty*. London: Penguin Books, 2002, p.101. Quoted by the authors.