Eminence or Evidence? The Volatility, Uncertainty, Complexity, and Ambiguity in Healthcare

"Where is the Life we have lost in living? Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?"

– T. S. Eliot in Choruses from the Rock

Today's digital revolution is forcing the healthcare practitioner to read too much, but learn very little. Contemporary knowledge systems have disintegrated into minutiae, focusing more and more on intricacies devoid of perspective. Scientific literature has become hopelessly fragmented and unmanageably voluminous. This is a double whammy. The digital deluge has shifted focus from primary to secondary sources, with the big picture getting further confounded by feel-good reports engineered by vested interests. Posttruth perceptions render health information inscrutable.

Creation of new knowledge has transformed too, with institutional priorities replacing individual aspirations and intrinsic creativity. Lure of money frequently dulls the edge of creative genius. The explosive growth of clinical data gives room for manifold interpretations. The greatest beneficiaries of this muddle are the powerful pharma companies that can interpret data conveniently into profitable publications. For instance, by deploying deceptive statistical tools such as "relative risk reduction," sponsors have been accused of creating a false impression of how cholesterol reduction by statins produces impressive clinical outcomes. Similarly, clinical trials sponsored by pharma majors have been accused ignoring adverse effects (AEs).

Problem is deeper than tweaking of published results. What about clinically relevant results that never get published? Everybody knows that negative results rarely get into a good journal. A recent paper on underreporting of AEs by Golder *et al*. in PLoS Medicine said that data searches from 15 databases, up to July 2016, showed AE reports were fewer in published papers than unpublished documents (median: 46% for published vs. 95% for unpublished). Authors conclude that published material would have excluded 43%–100% of the AEs, with a median of 64%. Moreover, unpublished reports listed more types of AEs than matched published reports.[1]

What about the negative results that concern the patient but did not see the light of day? Disturbingly, a meta-analysis that covered 48 papers showed that industry-sponsored studies more often had favorable efficacy results, risk ratios, and conclusions than those without sponsors.[2] Analyzing the efficacy of Tamiflu (Oseltamivir), it turned out that only those results that helped its marketing were visible.

Why do AEs emerge only after patent expiry? The Food and Drug Administration (FDA) and the pharmaceutical giants say that problems emerge only after millions of prescriptions are dispensed. A fairly convincing argument, but money changes human behavior. Lipitor (atorvastatin) the biggest blockbuster is supposed to have earned $125 billion in 15 years. Launched in 1997 when direct-to-consumer drug advertising started in the USA, more than 29 million Americans were prescribed Lipitor. Despite such a large number of patients taking Lipitor regularly and for so long, only in 2012, (when Lipitor patent expired) did FDA gather enough evidence to alert patients with labels warning of diabetes, liver injury, muscle damage, and memory impairment. Were adverse drug reactions so infrequent that they had to wait for decades to gather evidence for harm? Recent reports contradict this argument. Evidence is mounting on how statins reduce cholesterol but fail to improve cardiovascular outcomes. Atorvastatin is no exception. There are much more examples of AEs emerging after patent expiry. Paroxetine made $2.12 billion for GlaxoSmithKline in 2002, the year of patent expiry.

Adding to the inconsistent data on the dubious value of statins is the ambiguity on the hazards of cholesterol. A study on 70,000 patients did not establish a clear link between high low-density lipoprotein and mortality in older patients and premature deaths from cardiovascular disease. Ninety-two percent with high cholesterol lived longer. There are reports from Japan that reflect very similar outcomes. Prof. Sherif Sultan, University of Ireland, says, "…Lowering cholesterol for primary CVS prevention for patients older than 60 years is a waste of time… altering lifestyle is the single most important way to achieve a good quality of life."[3]

Following the above report that dumped statins, Lancet wrote that benefits of long-term statin treatment far outweigh the AEs, arguing that rare cases of muscle-related symptoms resolve quickly upon withdrawal, but heart attacks or strokes can be "devastating."[4] Retraction Watch discussed an open feud between Lancet and BMJ, culminating in BMJ refusing to retract papers that supposedly created a scare about statins by highlighting AEs.[4,5] Ben Goldacre, a popular whistleblower, physician, and science writer, in an interview, mentions how even top journals ignore inconsistencies between prespecified objectives at the time of clinical trial registration as well as in publishing outcomes of those trials. Even these "luxury" journals are not free from their own "publication bias."[6,7]

This takes us to the next problem of how clinical trials are executed. Randomized control trials (RCTs) on large populations are very expensive and cannot happen without a sponsor, who is invariably dependent on its clinical success. A careful examination will convince anybody that the clinical trial enterprise is managed by an oligopoly of "supertrialists"

who dominate the scene. One-third of all RCTs on antidiabetic drugs between 1993 and 2013 were published by 110 authors, who executed 991 RCTs with a median of 20 trials per author. Of these, 91% were commercially sponsored. Only 11 "supertrialists" wrote 10% of all articles and conducted 354 RCTs (media $n = 42$). "The burden of authorship should be distributed more equitably.…," says Dr. Frits Holleman, Academic Medical Center, Amsterdam. In other words, <1% of authors were responsible for one in three RCTs.[8]

Evidence generated by a few "key opinion leaders" from a few countries with considerable conflicts of interest is bound to be problematic. "There is a world-view that if science is paid for by a commercial interest that it is probably tainted and at least should be viewed with caution and… those people who have done that work should always be treated with suspicion of their motives," said John B Buse, MD, PhD, Prof. of Medicine and Chief of Endocrinology, University of North Carolina, Chapel Hill, USA.

Studies in the West show that 1–3 min with a medical representative increases brand-loyal prescriptions by 16%–52%; it could be worse in India. Major pharmaceuticals spend twice more on advertising than Research and Development. In 2007, when the NIH budget was $29 billion, companies spent $15–16 billion on marketing. "The combined profits ($35.9 billion) for ten drug companies in the Fortune 500 were more than the profits for all the remaining 490 in the list ($33.7 billion) in 2002," observed Marcia Angell, Former Editor of New England Journal of Medicine.

Profit rankings of pharma giants have fallen, probably because of a decline in pharmaceutical innovation. What could have caused this drop in new drug discovery? Pedro Cuatrecasas, who was himself a Lasker Awardee and had led the launching of several blockbusters, said that drug discovery is drying up because marketing and finance departments, not scientists guide the destiny of drug discovery programs. The stress is on predicting failure as soon as possible. Many blockbusters would have never seen the light of day if scientists did not play an active role. For instance, when cimetidine was being considered for treating gastric acidity, somebody is supposed to have raised an objection: "Who needs this H_2 thing when we have such wonderful antacids?" Cuatrecasas was involved in discovery, development, and marketing registration of more than forty drugs, which include zidovudine, acyclovir, salmeterol, gabapentin, and atorvastatin.[9]

The Food and Drug Administration Amendments Act, 2007 expanded the legal mandate for sponsors to include the publication of clinical trial results. However, of more than 224,000 study records in the clinical trial registry, only 23,000 display results say Zarin *et al*.[10]

All this unfortunate confusion reminds me of the volatility, uncertainty, complexity, and ambiguity (VUCA) steadily gaining currency in the business world. The pharma world fits in very well into the VUCA paradigm, with constantly changing norms and standards that paint a picture of greater uncertainty and complexity than any other professional domain. Are we slithering into an inescapable VUCA vortex, while those who practice the healthcare delivery system remain blissfully unaware of its potential hazards?

The take-home message is that even the most trusted journals are not infallible. Medical opinion is constantly changing. We must learn to question, challenge, doubt, and discuss issues with an open mind. Indian students, like many of our teachers, question very little but trust and obey authority too easily.

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