

Observational therapeutics: Scope, challenges, and organization

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ABSTRACT

The importance of Observational Therapeutics in the progress of medicine has been neglected in the current era of the hierarchical position imparted to Randomized Controlled Trials (RCTs) for new drug discovery and practice of evidence-based medicine. There is a need to reflect on the reason for many new drugs being withdrawn during post marketing surveillance. There are several examples in literature where drug-discovery has originated initially from keen clinical and / or laboratory observations. The roots of these discoveries have often been from observations made by practitioners of traditional medicine including Ayurveda. The present article draws attention to the scope and challenges for observational therapeutics. There is an urgent need for the meticulous planning for a systematic organization of developing observational therapeutics, with a full understanding of its strengths and limitations.

Key words: Evidence-based medicine, hierarchy of evidence, observational studies

INTRODUCTION

Debate about the objective validity of observational studies continues at the current times in the era of randomized controlled trials (RCTs) and evidence-based practice of patient care.^[1-3] However, there is an emerging realization in favor of observational studies in view of the dilemma about RCTs.^[4-6] Vandembroucke JP, while describing two sets of medical views — discovery research and evaluative research — suggests that both views can co-exist in an investigator's mind, and emphasizes the importance of teaching both.^[1]

The outcome and alarming impact of a Women's Health

Initiative Study-randomized trial of the hormone replacement therapy (HRT), did cause a dilemma for the evidence-based practice of menopausal healthcare.^[5] These and the withdrawals of many drugs from the market during their post marketing surveillance have questioned the soundness of the hierarchy of RCTs.^[7-9] Although the realization for the need of observational studies has been surfacing in the current literature, the studies require standardization and quality in design, proper data collection, and application of appropriate statistics equally.^[10-13] Observational studies could be judged on the basis of the validity of causal associations on well-defined criteria.^[13] Some of the important criteria are dose-response relationship, temporal sequence, biological plausibility, and so on. The present article focuses on the scope and challenges of observational studies, in view of the current exclusive emphasis and dependence on RCTs in the universe of evidence-based medicine. Appropriateness of Observational Therapeutics within this universe is highlighted through illustrative examples that have led to paradigm shifts in the understanding of mechanisms of diseases or their management.

Possible methods for observational therapeutics

- Keen observations of bedside therapeutic hits
- Concern for serendipitous clinical findings by objective investigative assessment
- Case reports, Case series
- Consensual, congruent and concurrent validation

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methods

- Meticulous observations of adverse events
- Careful recording of drug effects

SCOPE AND CHALLENGES OF OBSERVATIONAL THERAPEUTICS

The current scenario of new drug discovery and development is fraught with a high attrition rate, prohibitive costs and a long delay to the market launch. Post marketing drug withdrawals have also increased since 1993, as the Prescription Drug User Fee Act (PDUFA) got enacted in 1992 in USA, and has been revised several times since, where FDA collects fees from drug manufacturing industries to review the applications of their new drugs.^[14] The act might have facilitated quick approvals for new drugs, but has jeopardized patient safety.^[15,16] Many serious adverse drug reactions (ADRs) including fatal ones have occurred during the post marketing phase of the newly introduced drugs.^[17] One has often heard about the warning against use of new drugs particularly if old efficacious drugs are still available for the indication in question.^[18] This warning is powerfully driven home when one carefully reads, 'The Vioxx Saga: Perspective on the Recall,' by William R. Ware.^[19] Use of Vioxx, Cox-2 inhibitor, had caused serious cardiovascular side effects; around 27,000 cases of myocardial infarction had occurred between 1999 and 2003. Post approval double blind RCT (phase 4) was done, where the upper gastrointestinal side effects of Vioxx were compared with those of Naproxen. Vioxx had shown better tolerability. RCTs often get limited by questions asked, but the other unanticipated observations get knowingly or unknowingly ignored. Preapproval RCTs require a smaller number of patients and selected group of patients as per the inclusion / exclusion criteria. Hence, side effects that occur with a low frequency like 1% are ignored or attributed to chance. However, if these observations made during RCTs are considered as signals^[20] and followed up subsequently in well-planned observational studies, tragedies like those of Vioxx could be averted.

Overemphasis on RCT / non-RCT dichotomy, promulgated by proponents of the so called evidence-based medicine need to be balanced by a deep understanding of the appropriateness of study-design in a given situation.^[1,21] The scope of observational studies is immense and complementary and at times superior to other modes of experimental studies. Meticulous observations made and recorded by ancient and not so ancient practitioners of traditional medicine reflect their unique clinical skills and soundness of pharmacological understanding.^[22-25] Minute details of drug-related toxicity, precautions and antidotes have been mentioned by experts like Vaman Ganesh Desai,

Mayaram Sundarji, and Gananath Sen. Vaman Ganesh Desai has detailed dose-related therapeutic effects, side effects, and adverse drug reactions of *Picrorrhiza kurroa*.^[22]

Patwardhan and Mashelkar in their seminal article have covered the dilemma and suggested the application of Reverse Pharmacology and Systems Biology to Ayurveda, for drug discovery.^[26-28] In my judgment, Ayurvedic Pharmacology-Epidemiology^[29] and Observational Therapeutics are antecedent endeavors to the aforesaid paths. It is only through the fruition of bedside therapeutic hits that organized drug development can emerge.^[30]

Bedside therapeutics is getting quite sophisticated with the availability of target markers for defining the outcomes. The scope of Observational Therapeutics gets immensely enriched due to the validation of serendipitous clinical findings by objective investigative assessment. However, a judicious and economical usage of advanced markers necessitates robust thinking of biological plausibility and rational understanding of *dravya-guna-vignyan*. For example, when neutropenia was reduced with *Tinospora cordifolia* (*glabra*) in patients on cancer chemotherapy, the serial assays showed a rise in Granulocyte Monocyte-Colony Stimulating Factor — a mechanistic validation of a clinical observation.^[31]

The major challenge in successfully commissioning observational therapeutics lies in a general lack of knowledge in basic pharmacology, *dravya-guna-vignyan* and a grasp of index cases in epidemiology. It is hoped that Observational Therapeutics at the bedside would make these domains functional and interesting. The inspirational impact of new hits and leads has to be shared at the institutional morning reports, grand rounds, continued medical education, and widely read journals.^[32,33] In an interesting case report of acute cervical pain syndrome due to *pragnyaparadha*, the authors offer an insight into an association between *vegavarodha* and disease causation.^[34] The journals need to adopt a more flexible approach to the documentation of case records / series, other observational studies, and letters to editors.^[35-37] It is heartening to witness the progressive continuation of two high profile, peer-reviewed, indexed journals from India, where practitioners and scientists of multisystem biomedicine have an opportunity to get a critical appraisal and reporting of their observations and research work.^[38,39] Some of the observations are made only on a single or a small group of patients and reported in peer-reviewed journals dedicated to case reports and case series.^[35] They may also be on the basis of observations of outcome measures reported by patients and verified by the physicians.^[40] The observation may be worthy of further exploration by a suitable clinical study. Ashok Vaidya has suggested diverse modes of validity; consensual, congruent,

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and concurrent.^[41] In a recent J-AIM publication Somik Raha makes a plea for choosing research methods that help the researcher in clarifying decisions about the action.^[42] The importance of reporting meticulously observed and diligently recorded findings in a patient or made by an astute clinician / clinical scientist cannot be overemphasized. Such case reports have contributed to new knowledge or even paradigm shifts in clinical medicine. *Vaidya* Vilas Nanal has emphasized bedside teachings for imparting sound clinical training.^[36] Vandenbroucke has said that case reports and case series are important in the progress of medical science.^[35] The author states that detecting an unexpected finding in a case or laboratory investigation could be the beginning of a discovery. Several examples are cited by the author where case reports and case series have led, not only to identifying new diseases, but also to their genetic or molecular mechanisms.

In Traditional Chinese Medicine (TCM), records of cases go back to millennia. The Chinese proverb says it all, “The palest ink is better than the best memory.” We often bemoan the lack of records in Ayurveda vis-a-vis TCM. We tend to forget that there are innumerable Ayurvedic periodicals going back to a century or more. These magazines cover case reports, side effects, and the like. We need to create data bases from these journals and books so as to assist and enhance Observational Therapeutics.

METICULOUS OBSERVATION OF DRUG EFFECTS AND CLINICAL INNOVATIONS

A few examples of meticulous observations and careful recording of drug effects are cited here, which have led to the understanding of basic physiological mechanism of regulation of prolactin secretion, etio-pathological mechanism of pituitary hyperplasia, and tumor formation in primary target endocrine gland deficiency, and a revolutionary change in the management of prolactinomas.

The etiology of pituitary hyperplasia and its tumor formation was proposed on the basis of primary endocrine gland deficiency and resolution of pituitary hyperplasia / tumors by the specific hormone replacement, for example, Pituitary sella enlargement with supra sellar clinical manifestations, in patients having primary hypothyroidism completely reversed to normality on thyroid replacement.^[43]

Proposal of hitherto unknown mechanism of regulation of pituitary prolactin secretion was made when concurrent occurrence of galactorrhea-amenorrhea and Parkinson-like syndrome were observed in a patient on alpramethyl dopa.^[44] Medical management of prolactinoma was

suggested in two hyperprolactinemic patients, when visual field defects normalized in temporal relation to declining levels of circulating prolactin with a dopamine agonist, bromocriptine.^[45]

The aforesaid examples remind one of the remarkable side effects observed by Kaviraj Gananath Sen when he demonstrated the antihypertensive activity of *Rauwolfia serpentina*, benth.^[23] The side effects were Parkinsonism, galactorrhea, depression, and peptic ulcer. Such a cluster was not understood until the inhibition of the reuptake of catecholamines by reserpine was demonstrated. The rest is history in terms of the watershed of new drugs modulating biogenic amines. Several other Ayurvedic plants have shown clinical effects much before the mechanisms and new paths for drug discovery have been unveiled.^[46] However, there are several tales of missed opportunities because of the absence of the organized approach of Observational Therapeutics.^[47]

ORGANIZATION OF OBSERVATIONAL THERAPEUTICS

Innumerable new bedside observations are a natural corollary when a massive clinical material is being followed up. Unfortunately, neither the medical nor the Ayurvedic education equips clinicians / *vaidyas* to document meticulously and report their new bedside findings effectively. Despite this the roots of many modern drugs lie in astute clinical observations. A plea is made to rapidly develop the skills, knowledge, and alert attitudes for organizing Observational Therapeutics in modern medical and Ayurvedic teaching hospitals. There have been recommendations made for the twelfth five-year plan to provide resources — faculty, training, research, and infrastructure — for Observational Therapeutics. Early attention will have to be on the priority diseases of national importance.

The academic niche of Observational Therapeutics is a moot point. A similar situation was also faced when clinical pharmacology was proposed in the academia. As a consequence; the growth of clinical pharmacology in India and abroad has not met with the expectations. Hence, right from the onset Observational Therapeutics needs to be an integral part of the undergraduate and postgraduate clinical training. There have been several articles on the development of observational skills at the bedside and its impact on new therapeutic hits. It is proposed to have a task force to develop, on a fast track, undergraduate and postgraduate modules for teaching of Observational Therapeutics. The program for *Vaidya-Scientist* can undertake a pilot project to develop the pedagogic tools.

Key Messages from this article

- Exclusive hierarchy of randomized controlled trials, along with evidence-based medicine, has largely eclipsed the significance of even valuable observational studies.
- Observational studies could be judged on the basis of the validity of causal associations on well defined criteria like dose-response relationship, temporal sequence, and biological plausibility.
- Inspirational impact of new hits and leads has to be shared at the institutional morning reports, grand rounds, continued medical education, and widely read journals.
- A judicious and economical usage of advanced markers necessitates robust thinking of biological plausibility and rational understanding of *Dravya-Guna-Vidnyan*.

CONCLUSIONS

Exclusive hierarchy of randomized controlled trials, along with evidence-based medicine, has largely eclipsed the significance of even valuable observational studies. Disproportionate emphasis on RCTs has also thwarted the cognizance of unusual, unanticipated, and novel clinical findings and their systematic pursuit. There is an urgent unmet need to revive and reinforce astute observational bedside skills for a creative synthesis of clinical science with emergent Life Sciences. The nature of organization of the trans-discipline of Observational Therapeutics will depend on the situational and biomedical plausibility of events exhibited by such prepared minds. Then evidence-based medicine will have a balanced emphasis on valid observations and controlled experiments.

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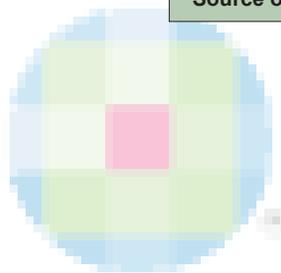
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