Observational therapeutics: Scope, challenges, and organization

Rama Vaidya

ICMR Advanced Centre for Reverse Pharmacology in Traditional Medicine, Medical Research Centre – Kasturba Health Society, Mumbai, India

ABSTRACT

The importance of Observational Therapeutics in the progress of medicine has been neglected in the current era of the hierarchal 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 There is a need to reflect on the reason for many new drugs being withdrawn during post marketing surveillance.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] Vandenbroucke 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.

Address for correspondence:
Dr. Rama Vaidya, Medical Research Center - Kasturba Health Society, 17, K. Desai Road, Vile Parle (W), Mumbai, India. E-mail: vaidya.rama@gmail.com

Received: 10-Nov-2011
Revised: 15-Nov-2011
Accepted: 22-Nov-2011

Access this article online

Quick Response Code:

Website: www.jaim.in

DOI: 10.4103/0975-9476.90764

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

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 Pharmaco-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,

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 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 pimary hypothyroidism completely reversed to normality on thyroid replacement.[43]

Proposal of hither to 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 alphamethyl dopa.[44] Medical management of prolactinoma was suggested in two hyperprolactinimic patients, when visual field defects normalized in temporal relation to declining levels of circulating prolactin with a dopamine agonist, bromoergocryptine.[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.

ACKNOWLEDGMENT

I thankfully acknowledge the continued guidance of Dr. Ashok Vaidya and creative assistance of Dr. Namyata Pathak in the preparation of this manuscript.

REFERENCES

1. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. PLoSMed 2008;5:e67.
2. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000; 342:1887-189
3. Guyatt GH, Rennie D. The evidence-based medicine working group. Users' guides to the medical literature: A manual for evidence-based clinical practice. Chicago: American Medical Association Press; 2002.
4. Harrisona GW. Randomisation and Its Discontents. J Afr Econ 2011;20:626-52.
5. Vaidya RA, Pandey SN. Estrogen therapy / hormone therapy: Post women's health initiative study dilemma, debate, and emerging consensus. ECAB CLINICAL UPDATE: Obstet Gynecol 2008;2:11-52.
6. Croft P, Malmivaara A, van Tulder M. The pros and cons of evidence-based medicine. Spine 2011;36:E1121-5.
7. Martin K, Bégaud B, Latry P, Miremont-Salamé G, Fourrier A, Moore N. Differences between clinical trials and postmarketing use. Br J Clin Pharmacol 2004;57:86-92.
8. Grossman J, Mackenzie FJ. The randomized controlled trial: Gold standard, or merely standard? Perspect Biol Med 2005;48:516-34.
9. Ligthelm RJ, Borzì V, Gumprecht J, Kawamori R, Wenying Y, Valensi P. Importance of observational studies in clinical practice. Clin Ther 2007;29:1284-92.
10. Krishnan E, Fries JF. Measuring effectiveness of drugs in observational databanks: Promises and perils. Arthritis Res Ther 2004;6:41-4.
11. Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. BMJ 2007;334:349-51.
12. Vandenbroucke JP. When are observational studies as credible as randomised trials? Lancet 2004;363:1728-31.
13. Grimes DA, Schul KF. Bias and causal associations in observational research. Lancet 2002;359:248-52.
14. Prescription Drug User Fee Act (PDUFA). US Food and Drug Administration of US Health Services - Official Website. Available from http://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/default.htm. [Last accessed on on 2011 Sep 27].
15. Friedman MA, Woodcock J, Lumpkin MM, Shuren JE, Hass AE, Thompson LJ. The safety of newly approved medicines: Do recent market removals mean there is a problem? JAMA 1999;281:1728-34.
16. Barclay L. Reform of postmarketing drug surveillance system needed. Medscape Medical News Nov. 30 2004
17. Roden DM. An unrecognized challenge in evaluating postmarketing drug safety. Circulation 2005;111:246-8.
18. Satoskar RS. Personal communication. 2005
19. Ware WR. The Vioxx Saga: Perspective on the Recall. International health news. Issue 153, December 2004. Available from: http:// www.yourhealthbase.com/Vioxx.htm [Last accessed on 2011 Nov 02].
20. Garrard E. Practical Approaches to lifecycle signal detection. Using the right tools to develop an ideal signal management system. FDA pharmaceutical and medical device training and conferences. Available from: http://www.fdanews.com/ext/files/Conference/RMDSS10presentations/Garrard-Practical%20Approaches%20to%20Lifecycle%20Signal%20Detection.pdf [Last accessed on 2011 Mar 22].
21. Hoppe DJ, Schemitsch EH, Morshed S, Tornetta P 3rd, Bhandari M. Hierarchy of Evidence: Where observational studies fit in and why we need them. J Bone Joint Surg Am 2009;91:2-9.
22. Desai VG. Kadu (Picrorhiza kurroa) in Aushadhi Sangraha. Vol 1. Jadhavji Trikamji Acharya.
23. Sen G, Bose K. Rauwolfia serpentina, a new Indian drug for insanity and hypertension. Indian Med World 1931;21:194-201.
24. Vaidya MS. Hadakavana ilajne vadhu pushti (More support for the remedy cited for hydrophobia). Vaidyakalpataru 1925;25:247-8.
25. Schwartz SA. Therapeutic intent and the art of observation. Jan 2009. Available from: http://www.schwartzreport.net/showarticle.php?id=6905 [Last accessed on 2011 Nov 02].
26. Patwardhan B, Mashelkar RA. Traditional medicine-inspired approaches to drug discovery: Can Ayurveda show theway forward? Drug Discov Today 2009;14:804-11.
27. Vaidya AD. Reverse pharmacological correlates of ayurvedic drug actions. Indian J Pharmacol 2006;38:311-5.
28. Patwardhan B, Vaidya AD, Chorghade M, Joshi SP. Reverse pharmacology and systems approaches for drug discovery and development. Curr Bioactive Compounds 2008;4:201-12.
29. Vaidya RA, Vaidya AD, Patwardhan B, Tillu G, Rao Y.

Ayurvedic pharmacoepidemiology: A proposed new discipline. J Assoc Physicians India 2003;51:528.
30. Vaidya AD. Reverse pharmacology – a paradigm shift for new drug discovery based on Ayurvedic epistemology. In Ayurveda in Transition. Arya Vaidya Pharmacy. Kottakal 2010
31. Thatte UM, Rao SG, Dahanukar SA. Tinospora cordifolia induces colony stimulating activity in serum. J Postgrad Med 1994;40:202-3.
32. Schiffman FJ. Morning report and work rounds: Opportunities for teaching and learning. Trans Am Clin Climatol Assoc 1995;107:275-86.
33. Miller G. In first Weill Cornell grand rounds, Dr. Skorton calls for greater collaboration and research into social aspects of medicine. Chronicle Online of Cornell University. 2007 Available from: http://www.news.cornell.edu/stories/Jan07 /skorton.grandrounds.html [Last accessed on 2011 Nov 02].
34. Pathak N, Raut A, Vaidya AB. Acute cervical pain syndrome resulting from suppressed sneezing. J Assoc Physicians India 2008;56:728-9.
35. Vandenbroucke JP. In defense of case reports and case series. Ann Intern Med 2001;134:330-4.
36. Nanal V. Are educational reforms needed? Ayurveda education Plenary Lecture-2, in Conclave proceedings. "Transforming traditions for tomorrow's health" Bhatt NS, editor. 2007. p. 36-40.
37. Shringi M, Vaidya R, Gogate J. Prolactin producing tumors in post menopausal patients–"Infrequent or Infrequently recognized". Fertil Steril 1998;69:603-5.
38. Thatte U. Editorial. Int J Ayurveda 2011;2:1.
39. Patwardhan B. Ayurveda and integrative Medicine: Riding a tiger. J Ayurveda Integr Med 2010;1:13-5.
40. Rothrock N, Kaiser KA, Cella D. Developing a valid patient-reported outcome measure. Clin Pharmacol Ther 2011;9:737-42.
41. Vaidya AD. An advocacy for Vaidya-Scientists in Ayurvedic research. J Ayurveda Integr Med 2010;1:6-8.
42. Raha S. A critique of statistical hypothesis testing in clinical research. J Ayurveda Integr Med 2011;2:105-14.
43. vanWyck JJ, Grumbach MM. Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism. An example of hormonal overlap in pituitary feed back. J Pediatr 1960;57:416.
44. Vaidya RA, Vaidya AB, Van Woert MH, Kase NG. Galactorrhea and Parkinson-like syndrome: An adverse effect of alpha-methyldopa. Metabolism 1970;19:1068-70.
45. Vaidya RA, Aloorkar SD, Rege NR, Maskati BT, Jahangir RP, Sheth AR, *et al*. Normalization of visual fields following bromocryptine treatment in hyperprolactinaeimic patients with visual field defects. Fertil Steril 1978;29:632-6.
46. Vaidya AB, Vaidya RA. Roots of modern drugs in Reverse Pharmacology. Med Update 2010;20:871-4.
47. Jain S, Murthy P. The other Bose: An account of missed opportunities in the history of neurobiology in India. Curr Sci 2009;97:266-9.

How to cite this article: Vaidya R. Observational therapeutics: Scope, challenges, and organization. J Ayurveda Integr Med 2011;2:165-9.

Source of Support: Nil, **Conflict of Interest:** None declared.