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Ayurpharmacoepidemiology en Route to Safeguarding Safety and Efficacy of Ayurvedic Drugs in Global Outlook

Parikshit Debnath, MPhil (Public Health), MD (Ayurveda)[1], Subhadip Banerjee, MPharm (Ayurveda)[1], Anjan Adhikari, MD (Pharmacology)[2], and Pratip K. Debnath, PhD, MD (Ayurveda)[1]

Abstract

Ayurpharmacoepidemiology is a new field developed by synergy of the fields of clinical pharmacology, epidemiology, and ayurveda. It will use the effects of ayurvedic medicinal products on large populations to describe and analyze the practices, evaluate the safety and efficacy, and carry out medicoeconomic evaluations. Good pharmacoepidemiology practices in ayurveda is projected to assist with issues of ayurpharmacoepidemiologic research. The embraced good pharmacoepidemiology practices guideline in this viewpoint will be able to provide valuable evidence about the health effects of ayurvedic herbs/drugs and consider different fields like pharmacovigilance, pharmacoeconomics, and drug discovery with ayurvedic reverse pharmacology approach, also pass out significant data for further basic sciences study in ayurveda biology, ayurgenomics, ayurnutrigenomics, and systems biology. Several unanswered questions about ayurvedic drug use and informed interventions or policies that can be addressed by informatics database, which will eventually demonstrate the credibility and rationality of ayurceuticals in the future.

Keywords

ayurpharmacoepidemiology, good pharmacoepidemiology practices in ayurveda, ayurvedic herbs/drugs, pharmacovigilance

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Evidence of increased cost of medication, polypharmacy, chronic diseases, and approval of advanced drug therapies are trending topics.[1,2] Thus, clients, policy makers, pharmaceutical establishments, government organizations, clinicians, and patients are all interested in drug products that are cost-effective, comparative-effectiveness research, encouraging evidence-based medicine to ensure patients receive quality care, and are focused on helping patients use medications appropriately.[3] Agreed-upon needs to study the use of drugs in the factual domain, continuous surveillance of drug use, and ways to evaluate how patient characteristics influence drug utilization and clinical outcomes in large populations can be met through the use of pharmacoepidemiologic research designs.[4] Pharmacoepidemiology deals with studies quantifying drug use patterns and adverse drug effects[4-6] by binding clinical pharmacology with epidemiology to study of the effects of drugs in human population.[7]

Traditional medicine is widely used by one-third of the world's population. Reported common reasons of using traditional medicine are more affordability, compliance with the patient's ideology, and being less paternalistic than allopathic medicine. Since, more than 50% of poorest Asian and African population does not have regular access to essential drugs; traditional medicine provides an important health care service to persons both with and without geographic or financial access to allopathic medicine.[8] Plant materials are used throughout developed and developing countries as home remedies, over-the-counter drug products, and raw materials for the pharmaceutical industry, and represent a substantial proportion of the global drug market. The World Health Organization emphasizes evaluation of the quality, safety, and efficacy of medicinal plants, ensuring rational use of plant-based products in an integrated approach.[9,10] As a matter of fact, Indian ayurveda, the ancient science with its unique fundamental principles and systematic approach documents a diversity of health care practices

[1] Gananath Sen Institute of Ayurvidya and Research, Kolkata, India
[2] R. G. Kar Medical College and Hospital, Kolkata, India

Corresponding Author:
Parikshit Debnath, MPhil (Public Health), MD (Ayurveda), Public Health Consultant, Gananath Sen Institute of Ayurvidya and Research, Kolkata 700037, India.
Email: docdebnath84@gmail.com

incorporating plant, animal, and/or mineral-based medicines (wide range of herbs, polyherbal formulations, herbomineral preparations), spiritual therapies, manual techniques, and exercises, applied singly or in combination to maintain well-being, as well as to treat, diagnose, or prevent illness.[11] Although further research, clinical trials, and evaluations are needed, ayurveda has shown great potential to meet a broad spectrum of health care needs.

Concept of Ayurpharmacoepidemiology

There is a widespread misconception that all drugs of "natural" origin are "safe." There is also a common belief that long-term use of a medicine based on tradition, assures both safety and efficacy. Currently, the majority of adverse events related to the use of herbal/traditional products that are reported are attributed either to poor product quality or to improper use.[12,13] Recognizing the widespread use of ayurvedic medicine and the tremendous growth of international markets for herbal products, it is important to ensure that the health care provided by ayurveda is safe and reliable; that standards for the safety, efficacy, and quality control of ayurvedic products and therapies are recognized and endorsed; that practitioners have the qualifications they acknowledge; and that the statements made for products and practices are legal. The practice of ayurvedic pharmacotherapy may offer many challenges to clinicians as they are not aware of the potential benefits, efficacy, and risks of ayurvedic drugs to individual and population-based patient care. It is not realistic to believe that large, prospective clinical trials can be conducted to understand all issues of ayurvedic medication use in large populations. There are limited financial resources to conduct large clinical trials for every drug in various subsets of populations. Many unanswered questions about ayurvedic drug use remain and informed interventions or policies are yet to be addressed. Thus ayurpharmacoepidemiology is a new discipline that can be a viable alternative to address those questions.[11,14]

Pharmacoepidemiology is the study of the utilization and effects of drugs in large numbers of people. It provides an estimate of the probability of beneficial effects of a drug in a population and the probability of adverse effects, that is, phase IV clinical trial postmarketing surveillance. It can be called a bridge science spanning both clinical pharmacology and epidemiology. Pharmacoepidemiology concentrates on clinical patient outcomes from therapeutics by using methods of clinical epidemiology and applying them to understanding the determinants of beneficial and adverse drug effects, effects of genetic variation on drug effect, duration-response relationships, clinical effects of drug-drug interactions, and the effects of medication nonadherence. Pharmacovigilance is a part of pharmacoepidemiology that involves continual monitoring, in a population, for unwanted effects and other safety concerns arising in drugs that are already on the market. Pharmacoepidemiology sometimes also involves the conduct and evaluation of programmatic efforts to improve medication use on a population basis. Pharmacoepidemiology research is often based on large health care utilization databases using nonexperimental study of intended and unintended drug effects outside of randomized controlled trials. In this context, ayurpharmacoepidemiology is defined as "the study on the use of and the effects of ayurvedic herbs/drugs in large numbers of people with the purpose of supporting a rational and thereby cost-effective use of safe and effective ayurvedic herbs/drugs in the population." The field of ayurpharmacoepidemiology will use the effects of ayurvedic medicinal products on large populations in order to describe and analyze the practices and conditions of use, evaluate the safety and efficacy as an alternative to a clinical trial (including pharmacovigilance surveillance), evaluate the effectiveness in a routine situation ([comparative] effectiveness research), and carry out economic and medicoeconomic evaluations.[11,15-17]

Throughout India, different disease patterns occur in different region, so also use of ayurvedic formulation is different according to different agroclimatic zone for same disease. Difference lies in use of a formulation, use of different herbs nomenclature (Brahmi, Daruharidra, Rasna, etc), the different pharmaceuticals, and preference for over-the-counter drugs of which company (Chyawanprasha, Lavan Bhaskar, Arista). Ultimately, whether there are any adverse drug reactions in relation to ayurvedic diagnosis needs further study. The preliminary study will form the basis for large sample survey in Indian context. Like the recent studies conducted on Socioeconomic Survey by the National Sample Survey Office, Ministry of Statistics and Programme Implementation, Government of India, to know how far Indian people are dependent on ayurvedic drugs.[18] Thus, ayurpharmacoepidemiology will be a starting point for further reverse pharmacology research.

Ayurpharmacoepidemiology research is one such technique that can be implemented to acquire facts about ayurvedic medication practice and safety without having to invest in large clinical trials. Ayurpharmacoepidemiology study can be less expensive and provide some evidence as to the use and safety of ayurvedic medications in populations. By combining the interest of ayurveda, pharmacology, and epidemiology, an ayurpharmacoepidemiologist will apply epidemiological principles to study the effects of ayurvedic medications/medicinal herbs in human populations. Ayurpharmacoepidemiology studies will quantify ayurvedic drug use patterns and adverse ayurvedic drug effects, including common predictable adverse drug reactions as well as the uncommon and unpredictable ones.[16,17]

Ayurpharmacoepidemiology will emerge out as a new branch of AYUSH (Reverse Pharmacology, Ayurveda, Siddha, Unani) to meet the needs of World Health Organization's South-East Asia Regional Office charter on traditional medicine development during 2014-2023.[9] It is the need of the day to substantiate the global need on the use of ayurvedic drugs backed by evidence to fulfill the regulatory norms for wide acceptance. In order to meet the good clinical practices competence of the ayurceuticals, this may be a reverse way similar to the phase IV postmarketing surveillance of clinical trial. Ayurpharmacoepidemiology will create an informatics database in a reverse way to substantiate and point out the success as well as

lacunae of the ayurvedic drugs. It is equally important for safety and quality assurance of the drugs, specifically when ayurvedic drugs are facing international criticism for heavy metal toxicity. This is like a postmarketing surveillance to record adverse events for ayurvedic drugs (composed of polyherbal pharmaceuticals), which have been used for thousands of years. Even single herbs contain multiple molecules. Clinical trial of all the ayurvedic formulation used throughout India will be a time-consuming process requiring huge finance. In order to note its adverse events as well as efficacy, if any, to record it in populations may help in compliance of regulatory norms in accordance with World Health Organization traditional medicine drug standardization, mechanism, and toxic component.[12,13,19]

Good Pharmacoepidemiology Practices in Ayurveda

Pharmacoepidemiology is being used progressively to appraise health care systems, interventions, and health-related behaviors. It is the scientific mainstay of assessing a drug's benefits and risks, and developing, executing, and assessing strategies to enhance the overall balance of such benefits and risks. The International Society of Pharmacoepidemiology identified pharmacoepidemiologic research as the study area where uses and effects of health care products expanding to clinical, economic, and other health outcomes are measured. The International Society of Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices are intended to assist investigators with issues pertaining to the planning, conduct, and evaluation of pharmacoepidemiologic research.[19]

The adopted good pharmacoepidemiology practices guideline addresses areas such as protocol development; responsibilities, personnel, facilities, resource commitment, and contractors; study conduct; communication; adverse event reporting; and archiving.[19,20] In light of this, ayurpharmacoepidemiologic studies may be able to provide valuable evidence about the health effects of ayurvedic herbs/drugs. These may be helpful in different domains like pharmacovigilance, pharmacoeconomics, and drug discovery with ayurvedic reverse pharmacology approach. The important areas where ayurpharmacoepidemiology may deliver are drug safety, pharmacovigilance, and risk management of ayurvedic, siddha, and unani drugs; regulatory affairs—drug safety and pharmacovigilance of ayurvedic, siddha, and unani drugs; health economics (pharmacoeconomics related to ayurvedic, siddha, and unani medicine); exploratory and confirmatory clinical development; clinical trials (reverse pharmacology) of ayurvedic, siddha, and unani drugs; nonclinical testing, pharmaceutical and early clinical development; and special populations—clinical trial practice and regulation of ayurvedic, siddha, and unani drugs; project management in ayurvedic, siddha, and unani medicines development.

Good pharmacoepidemiology practices in Ayurveda will assist researchers in following good ayurpharmacoepidemiologic research principles, including the use of ayurpharmacoepidemiologic studies for risk management, events of ayurvedic herb/drugs; promote comprehensive ayurpharmacoepidemiologic research by encouraging arduous data collection, analysis, and reporting; provide a framework for conducting and evaluating ayurpharmacoepidemiologic studies; facilitate suitable use of technical resources by inspiring vigilant study design and planning of study conduct. This in turn will help in understanding the usage of ayurvedic medicines (generic/proprietary), their safety novel beneficial effects as well as adverse events/effects. It will also capture new indications for a given plant/drug and serve as the major resource for reverse pharmacology.

Clinical Trial and Good Clinical Practices of AYUSH

Several documents of the World Health Organization like the General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine, Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines can be followed while designing the clinical trial for Ayurvedic drugs.[19,21,22] Recently, in 2013, Ministry of AYUSH, Government of India has published an "AYUSH Good Clinical Practice Guideline" for clinical trial to evaluate safety and efficacy of ayurvedic drugs.[23] The guideline is now assigned a voluntary status and open to discussion about feasibility and rationalization issues about clinical ethics. It is presumed that new ayurvedic drugs apart from classical preparation included in the essential drug list of ayurvedic drugs have to undergo such clinical trial before they are marketed. Clinical trials should include a test and a control group with statistically significant large population. Single case studies, add-on designs, and quality-of-life studies should be undertaken in case of diabetes. Clinical trials should be designed to bring out meaningful data for further basic sciences study in ayurveda biology, ayurgenomics, and systems biology. This will help us identify novel targets and even biomarkers for further drug research. Variation of drug response across *prakriti* types and their genome-wide associations should be studied, which will develop deeper understanding about ayurpharmacogenomics. This translational approach will eventually bring out new edge in natural product–based drug discovery and personalized medicine in ayurveda.

Pharmacovigilance in Ayurveda

Inclusion of ayurveda in pharmacovigilance systems has become increasingly important given the growing use of ayurvedic products and medicines globally. Pharmacovigilance of ayurvedic herbs/drugs can be stated as "the detection, assessment and prevention of adverse drug reactions from ayurvedic origin in humans." The process monitors ayurvedic medicines as used in everyday practice to identify previously unrecognized adverse effects or changes in the patterns of their adverse effects; assessing the risks and benefits of ayurvedic medicines in order to determine the obligatory actions to expand their safe

use; providing information to users to optimize safe and effective use of ayurvedic medicines; and monitoring the impact of actions taken.[12] Ayurveda advocates the personalized methodology in treating patients. Furthermore, instead of using single therapeutics, ayurveda uses combinatorial therapy, which is more complex in nature. Systematically determined seasonal and daily regimes, including lifestyle modification and ayurvedic dietetics based on ayurvedic *prakriti* (phenotype) are the unique features of ayurvedic management, known as ayurnutrigenomics.[24,25]

Ayurveda has long-lasting historical substantiation of safety and efficacy of cures adjudicated in terms of its particular endpoints. This strong experiential evidence may be considered in ayurveda's support. It is reasonable to arbiter the success of ayurvedic treatments in terms of ayurvedic endpoints and not be restricted to endpoints designated by the biomedicine approach. The ayurvedic system of medicine has endured and flourished over an extensive period of time, which is a signal that it works. Better record keeping tracking the effectiveness and safety of the therapeutic regimen sustained by a vigorous pharmacovigilance program is already taking place. The ayurvedic pharmacovigilance program should focus more on effectiveness rather than on safety, as is the case with conventional medicine databases. The conceptual framework for new models of ayurvedic clinical studies and guidelines for AYUSH Good Clinical Practices have stemmed from the principles and practices of Ayurveda.[26] If practized properly, the global scientific community should also benefit.

Future of Ayurpharmacoepidemiology: A New Beginning

The proposed guidelines give the impression to have been one up on the basis of conventional biomedical tactics, including randomized controlled trials as necessary evidence. These are primarily related to evaluation of New Chemical Entities.[27] Further attention to the special needs of the ayurveda, siddha, and unani sector is necessitated. Observational studies, meta-analyses, case studies and case series, and an effective pharmacovigilance program are much more in keeping with the needs of the situation. Also, as a body of knowledge they are technically unbiased. Thus, rather than performing randomized controlled trials of Ayurveda managements, future research efforts must focus on ayurpharmacoepidemiological research, which will take account of full-bodied documentation and accepting their contrivances and prominence as a reasonable and safe health care system. Since safety of the materials is already established from traditional use track record, pharmaceutical development, safety validation, and pharmacodynamic studies in parallel to controlled clinical studies must be underrtaken. Thus, drug discovery based on ayurveda follows a ''reverse pharmacology'' path from clinics to laboratories (bedside to bench approach). Ayurpharmacoepidemiology will ensure safety and efficacy by recording the ongoing use among populations, which has been there for almost 5000 years. There is a need of high-throughout informatics database that will ultimately prove the credence and rationality of ayurceuticals for a better tomorrow.

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Author Contributions

PD and SB contributed to concept designing, manuscript preparation, and review of literature. AA contributed to concept designing and monitoring. PKD contributed as a mentor and to integrative concept designing.

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