



## Review Article

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### NEED OF PHARMACOVIGILANCE IN AYURVEDA: A REVIEW

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#### ABSTRACT

Pharmacovigilance is defined as the activities relating to detection, evaluation, understanding and prevention of adverse drug reactions or other drug related problems. WHO established its programme for International Drug monitoring in response to thalidomide disaster detection in 1961. In India, even though The National Pharmacovigilance Programme has organised a separate area for ASU drugs, lack of knowledge about the concept and importance of pharmacovigilance among ayurvedic practitioners leads to the improper analysis and report of adverse effects. In case of ayurvedic drugs there is a popular misconception that they are devoid of adverse reactions. But in reality, side effects are not completely absent but they are comparatively less. In addition to this, with the increase in demand of herbal drugs, Ayurvedic drug manufacturing companies are sprouting in every nook and corner leading to the compromise in the quality of the medicines. This can have a profound impact on the safety and efficacy of ASU drugs in the market. Further application of causality assessment scales for ayurvedic medicines is perhaps the greatest challenge due to several reasons. This paper aims to assess the need of pharmacovigilance in Ayurveda.

**Key words:** National Pharmacovigilance programme, ASU drugs, Adverse reaction

#### INTRODUCTION

There are many evidences, showing the huge effect of poor quality, adverse drug reactions and medication errors on health care. But actual impact of this problem is impossible to calculate, since most cases go undetected. Most of the evidences are available from developed countries. A follow-up report estimated that more than 1.5 billion Americans are injured every year by medication errors in hospitals, nursing homes and doctor's office<sup>1</sup>. In the case of low and medium income countries, the situation is more urgent because of the poorer state of health system infrastructure and lack of essential study reports. Hence the importance of pharmacovigilance arises for addressing the product quality, adverse drug reaction (ADR) and medication errors.

Adverse Drug Reaction significantly diminishes quality of life, increases hospitalization and mortality<sup>2</sup>. Presentation of ADRs along with the disease makes it complex. New drugs are being approved for marketing without much long-term safety studies. In a new drug development process many stages are there involving chemical studies, animal studies and human studies for evaluating the safety and efficacy. But after the product is approved, it may have been tested in only thousands of patients – many fewer than are likely to use the product once it is approved for sale on the market. So, the information on effects generated in premarketing studies is incomplete relative to the full complement of likely users, making post-marketing surveillance an important tool for completing the safety and efficacy profile of a drug product<sup>3</sup>. This is a part of phase 4 clinical study as per ICMR ethical guidelines.

The National Coordinating Council for Medical Error Reporting and Prevention defines medication error as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health

care professional, patient or consumer”<sup>4</sup>. These are caused by faulty system, process and conditions that lead people to make mistake or fail to prevent mistake. Other problems can result from illegible handwriting, use of dangerous abbreviations, overlooked interactions with other medicines and verbal miscommunications and sound-alike or look-alike products. These errors should be preventable through education and effective system controls involving pharmacists, prescribers, nurses, administrators, regulators and patients.

Multi-national marketing makes it riskier because the drug can be made available easily and widely within the short period of time. The WHO set up its international drug monitoring programme after the Thalidomide disaster. Since 1978, the programme has been carried out by Uppsala Monitoring Center (UMC) Sweden. Emphasizing patient safety, it started Pharmacovigilance programme at global level. The WHO defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problems”. An Adverse Drug Reaction (ADR) is a harmful response in the patient caused by the drug itself given in the recommended manner (dose, frequency, route and administration technique). WHO defines a serious ADR as any reaction that is fatal, life-threatening, or permanently or significantly disabling; requires or prolongs hospitalization; or relates to misuse or dependence (WHO/UMC 2000). WHO promotes country level Pharmacovigilance programmes and by 2010, 134 countries were part of this programme.

#### STEPS IN PHARMACOVIGILANCE PROGRAMME

**Data collection** – This can be passive data collection, mandatory data collection or active data collection. Passive reporting of ADRs and medication errors (also known as voluntary case reporting) requires health care providers to be active participants in a culture of safety. This helps to establish a team approach to

improve patient care and reducing risks. Mandatory data collection mainly deals with the data reported by manufacturers and distributors during post marketing surveillance under strict regulations. Active data collection is carried out as a focused and structured activity and includes trigger tools, patient chart audits and direct observation methods.

**Data management** – Mainly deals with analysis and reporting. Specific algorithms and classification systems has been developed for these analysis and reporting should be in specific forms.

**Signal Detection** – A signal consists of reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely reported previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of information. Each detected potential signal will undergo further evaluation. The National Drug Advisory Committee is provided summary information for evaluation. The committee recommends what action needs to be taken, i.e. if it is a signal that needs to be acted upon, no signal, or if further monitoring is needed. Signals related to medication errors will be evaluated to determine whether preventative actions can be made. Depending on the nature of the safety concern, assessment will be performed in collaboration with the MAH or health facility. Product quality problems are communicated to the relevant directorates at the authority for testing.

**Safety issue assessment & Decision making** - When a signal has been confirmed, action is taken by

- Letters to healthcare providers about the safety concern describing how it may affect present patients on the medicine and future prescribing. The action needed might only be a warning of a possible safety concern that have been detected and may recommend a continued vigilance in prescribing and dispensing the medicine.
- Package insert revisions – when safety concerns become significant, manufacturers must change the label of the product. This action requires changing the official labelling and changing the package insert to reflect the new safety concern. Regulatory officials typically approve the change.
- Modifying inadequate designs of product labelling, packaging, product formulation, medical device, or product/technical information.
- Medicine recalls – When the risk of ADRs or product quality issues outweighs the benefits, withdrawing the medicine from the market might be necessary. Medicine recall can be voluntary or imposed by regulatory authorities<sup>5</sup>.

## NEED OF PHARMACOVIGILANCE IN AYURVEDA

Although the technical term “Pharmacovigilance” does not feature in Ayurvedic texts, the spirit of pharmacovigilance is vibrant and is emphasized repeatedly in all major texts. The major goals of pharmacovigilance, namely to improve patient care and safety in relation to drug use, and thus promote rational drug use are recurrent themes of Ayurvedic pharmacology and therapeutics. The use of Ayurvedic medicines is popular in India - and in recent times has become accepted in other countries. A recent survey conducted by the NCCAM in the USA showed that about 751 000 people in the United States had ever used Ayurveda and 154 000 people had used them within the past 12 months. Associated with this increasing use, there are growing concerns about the safety of Ayurvedic medicines also<sup>6</sup>.

A popular misconception is that Ayurvedic medicines are devoid of adverse reactions. But the reality is far away from this. Side effects are comparatively less, but not absent. This is because as per Ayurvedic concepts the treatment is for the patients (Humans) and not for the disease. More over the medicines are not a single molecule or compound, but as a whole from a plant or animal origin. Several host-related factors to be considered while selecting medicines in order to minimize adverse reactions like the constitution of the patient (prakriti), age (vaya), disease (vikruti), tolerance (previous exposure) (satmya), psychological state (satwa), digestive capacity (ahara-shakti), capacity for exercise (vyayama shakti), quality of tissues (Sara), physical proportions of the body (sahanan) and strength (bala).

However, texts like Charaka Samhita, Susruta samitha and Ashtanga Samgraha, describes all the adverse reactions to medicines when they are prepared or used inappropriately. Attention is given to factors like the physical appearance of the part of the plant to be used (prakriti), its properties (guna), actions (karma; prabhava), habitat (desha), season in which it grows (ritu), harvesting conditions (grahitam), method of storage (nihitam) and pharmaceutical processing (upaskritam) while selecting the starting material that goes to form the medicine<sup>7</sup>. Many classical Ayurvedic formulations contain metals and minerals as medicines usually as bhasmas (incinerated mineral formulations) or in combination with plants as herbo-mineral formulations. Manufacturing procedures for these medicines are stringent, and adverse reactions are described when precautions are not taken while manufacturing and administering these medicines. Although these medicines are widely used in India, doubts about their long-term safety come up due to the presence of toxic metals in them<sup>8</sup> and there are reports related to adverse reactions<sup>9</sup>.

In ancient times, the Ayurvedic physicians prepared medicines themselves for their patients. Today, only a handful of practitioners follow this practice and production and sale of Ayurvedic drugs has become formalized into a thriving industry. Manufacture and marketing of Ayurvedic drugs is covered by the Drugs and Cosmetics Act, 1940. Hence two categories of medicines labeled as “Ayurvedic” are available in the market: classical Ayurvedic formulations and patent and proprietary formulations. Moreover, with increased use of drugs of these systems, the chance for adulteration, preparation of counterfeit drugs and development of formulations which do not have conceptual basis in these systems has increased. Further cultivation of medicinal plants with laboratory generated species is being attempted on the basis of chemical composition and is likely to be used in increased manner for commercial purpose. These changes may have profound impact on the safety and efficacy of the ASU drugs in the market.

## PHARMACOVIGILANCE IN INDIA

In 1986, first Adverse Drug Reaction monitoring system was proposed. India joined WHO-ADR monitoring programme in 1997 and the center in New Delhi (at department of Pharmacology, All India Institute of Medical Sciences) was identified as the national center while the center in Mumbai (at KEM) was identified as the WHO special centre. National Pharmacovigilance programme (NPVP) was launched in November 2004 with 2 zonal, 5 regional and 24 peripheral centers overseen by the National Pharmacovigilance Advisory Committee based in the Central Drugs Standard Control Organization (CDSCO)<sup>10</sup>.

## REGULATIONS FOR ASU DRUGS

In India, Pharmacovigilance programme for ASU drugs was established under Department of AYUSH, Ministry of Health and Family Welfare, Govt. of India. Institute for Post Graduate Teaching and Research in Ayurveda (IPGTRA), Gujarat Ayurved University Jamnagar is the National Pharmacovigilance Resource Centre for Ayurveda Siddha and Unani Drugs (NPRC-ASU). As per protocol, the NPRC-ASU Drug is coordinating this national Pharmacovigilance programme under AYUSH and also under the guidance of National Pharmacovigilance Consultative Committee for ASU Drugs (NPCC-ASU). NPCC-ASU comprises many of the administrative heads of National Institutes, regulatory authorities and technical persons. It is having the responsibility to monitor and regulate administrative and financial aspect to the programme. This programme is also supervised by National Pharmacovigilance Technical Advisory Committee (NPATC-ASU), for reviewing and analyzing the ADRs reported at different levels and to suggest proper remedial measures.

There are eight Regional Pharmacovigilance Centre (RPC) for ASU drugs and 30 Peripheral Pharmacovigilance Centre (PPC). All these are controlled and coordinated by NPRC-ASU drugs. Adverse drug reactions related to any ASU drugs being reported to these PPCs, in a specially designed ADR reporting form, will be transmitted upwards after proper evaluation at each<sup>11</sup>. For the proper functioning of this programme, awareness about the concept of Pharmacovigilance and how to report ADR should be there among the health professionals and professional associations. Department of AYUSH is conducting many CME and RoTP at national level for this. A web portal, [ayushsuraksha.com](http://ayushsuraksha.com) has also been launched for online registration of ADR related to ASU drugs through an 'e format'.

### What to report under NPP-ASU?<sup>12</sup>

The programme particularly solicits reporting of

- All ADR suspected to have been caused by ASU drugs either alone or in conjugation with other drugs
- All suspected interactions
- Reactions to any other drugs suspected of significantly affecting a patient's management, including reactions suspected for events in the following categories

1. Death
2. Life threatening (real risk of dying)
3. Hospitalization (initial or prolonged)
4. Congenital anomaly
5. Required intervention to prevent permanent impairment or damage.

### Who can report?

Any health care professional may report suspected adverse drug events. The case reported by lay members of the public, or non-health care professionals are not accepted under the programme. But they can report the physician under whom they have undergone treatment<sup>12</sup>.

Sources of reports<sup>13</sup>

- Clinical trials
- Spontaneous reports
- Reports from consumers
- Reports from manufacturer

- National Poison center
- Drug information center
- Consumer organization

### Where to report?

Reporting should be done in a prescribed format through a local Pharmacovigilance centre<sup>14</sup>.

Progress of Submitted information - The peripheral pharmacovigilance centers forward the confidential forms to their regional centers, where casualty analysis is carried out. The information is then forwarded to the National Pharmacovigilance Resource Centre, where it is consolidated, statistically analyzed, and forwarded to the department of AYUSH.

## CHALLENGES IN AYURVEDIC MEDICINES

Although, National Pharmacovigilance Programme has encouraged and even a separate area for ASU drugs has been organized, the number of adverse reactions to Ayurvedic drugs reported or recorded in India is negligible. The strong belief that Ayurvedic medicines are safe contributes to a large extent to this situation. Patients are not adequately aware that Ayurvedic medicines can cause adverse reactions and can take medicines for years on end with no monitoring as they believe that these medicines can do no harm. Hence, they do not even give history of taking these medicines. There is another false belief that the Ayurvedic drugs are not having any expiry date even though this factor has been taken care of by introducing a rule regarding the shelf life<sup>15</sup>. Although several scales are available for causality assessment, applying them for Ayurvedic medicines and ascribing causality is perhaps the greatest challenge for several reasons, including:

1. Lack of knowledge about the concept and importance of pharmacovigilance in Ayurveda among Ayurvedic practitioners
2. Pharmacovigilance terms & monitoring are not covered in the Ayurvedic curriculum
3. Methods to study drug safety problems have not evolved adequately in Ayurveda, signal detection is difficult because there is an inherent belief about safety of Ayurvedic medications leading to lack of reporting and collection of reports relating to any formulation
4. Lack of quality assurance and control in manufacture of Ayurvedic medicine and the problem of counterfeit and spurious drugs and controversial drugs.
5. Information related to adverse effects is scattered in Ayurvedic literature and not in electronic form, hence making it difficult to access.
6. Most Ayurvedic formulations are multi-ingredient-fixed dose formulations rarely prescribed alone.
7. Additionally, there is the confounding factor that the patient is often receiving allopathic medicines at the same time.
8. Dose-related responses are rarely measured and reported.
9. Rarely, if ever, is de-challenge and re-challenge performed and there is no objective evidence of the adverse event.
10. One of the most challenging aspects is the lack of expertise in performing causality analysis with Ayurvedic medicines. A person trained in pharmacovigilance rarely understands Ayurveda while an expert in āyurveda is not trained in the science of pharmacovigilance.

## RECOMMENDATIONS

There are several ways we can move forward in attempting to up-to-date the pharmacovigilance systems for Ayurvedic drugs.

Some of them are,

1. Concepts of pharmacovigilance should be included in the curriculum itself.
2. Studies on drug safety should be encouraged with strict implementation of regulations related to collection, manufacturing, preservation, dispensing and ethical guidelines.
3. Reporting of adverse reactions to regulators should be made mandatory.
4. Unbiased and easily accessible drug information should be made available like TKDL.
5. Regular awareness programmes should be conducted among practitioners, patients and paramedical staffs.
6. A validated scale should be developed for the reporting of ADR on the basis of Ayurvedic principles.

### CONCLUSION

The need of the hour is to educate the physicians and encourage them to analyze and report any adverse effects that occur in a patient, no matter how petty or irrelevant they may seem. Quality drugs are one of the main pillars of effective therapy. The onus of providing quality drugs lies with the pharmaceutical houses. The industry should take some concrete steps to generate confidence and reliability for its products. The morality of manufacturing standard drugs can go a long way in minimizing the adverse effects and generating confidence in therapeutic efficacy. Further, this shall in long term lead to characterization of Ayurvedic drugs as OTC (over the counter), prescription or scheduled drugs for better safety and acceptance of Ayurvedic medicines. At some stage, there also needs to be regulation of self-preparation and administration of drugs by clinician. This shall only be a step towards global acceptance of Ayurvedic drugs.

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