DISCUSSION

The importance of pharmacovigilance is the ongoing assessment of the safety of a marketed medicine which has been increasingly appreciated in recent years, owing in part to high-profile safety issues with widely used drugs making Pharmacovigilance an integral part of drug therapy. It aims at making the best use of medicines for the treatment or prevention of disease. Good pharmacovigilance will identify the risks and the risk factors in the shortest possible time so that harm can be avoided or minimized. When communicated effectively, this information allows for the intelligent, evidence-based use of medicines and has the potential for preventing many adverse reactions. This will ultimately help each patient to receive optimum therapy, and on a population basis, will help to ensure the acceptance and effectiveness of public health programmes.

Significant harm to a few patients can destroy the credibility, adherence to and success of a programme. Rumors and myths about the adverse effects of medicines can spread rapidly and are difficult to refute in the absence of good data. Pharmacovigilance can provide this data. Good pharmacovigilance practice can generate the evidence that will inspire public confidence and trust. Pharmacovigilance incorporates and provides training in the identification of adverse reactions, data collection, processing and analysis. The information collected also provides the tools for the effective management of problems. These include communication and minimization of risk. In various studies, adverse drug reactions have been implicated as a leading cause of considerable morbidity and mortality.
In spite of this it is not widely practiced in Indian hospitals. The idea that pharmacovigilance programme can be setup and effectively implemented only in the developed countries should be replaced by the realization that a reliable system of pharmacovigilance is extremely essential for the rational, safe and cost-effective use of medicines even in developing countries like India. Such a mindset would go a long way in improving the quality and safety of patient care.

**Part 1: Development of a Pharmacovigilance Programme**

Blue print for developing Pharmacovigilance programme involves Risk Minimization, Risk Assessment and Analysis of Pharmacovigilance data.

**A. Risk Minimization**

The first and the most important step at the outset for the successful development of Pharmacovigilance programme is Risk minimization. It comprises of training and safe care delivery.

There are different methods for training which includes classroom lectures, discussions, case studies, role playing, videotapes/slides etc. These methods are regularly used for training patients as well as health professionals. However there are some challenges and disadvantages associated with them. Direct classroom teaching, though effective the communication could be one-way, content may vary from person to person and participants may lose interest if the speaker is not a good orator. Discussion method is not practical with more than 20 health professionals; some health professionals may not participate, the process is time-consuming and can meander. In the case study method,
the case must be clearly defined or insufficient information can lead to inappropriate results.

Videotapes/slides method is an entertaining way of introducing content and raising issues, keeps the group's attention and stimulates discussion for teaching patients, health workers and health professionals.

Thus keeping in mind the above points, the video training method for pharmacovigilance was thought to be better than the other methods. It helps to hold the attention of the target audience, human variation during the information delivery process can be eliminated as the video provides the same amount of information which is reproducible and there is no need for an experienced trainer. This method also helps to deliver information about the disease, the appropriate use of the drug, and the preliminary treatment of side effects to the illiterate patients, as well as health workers and doctors from remote parts of country where it becomes difficult to reach them.

A documentary for **Pharmacovigilance for Visceral Leishmaniasis in India, Nepal, Bangladesh** was conceptualized and developed in collaboration and with funding from the World Health Organization Tropical Diseases Research (WHO-TDR), Geneva, Switzerland.

The DVD was well accepted and it was appreciated for delivering maximum information in simplified language over a short time. The observations of the pre and post test scores revealed that there was an immense improvement in all 3 target groups (physicians, patients and health care workers) about the knowledge of disease, treatment, ADRs which
are commonly encountered during the course of the therapy and accurate reporting of the ADRs.

In a typical rural setting in our country where PHC’s are widely dispersed across villages, ASHA health care workers play a vital role working at the grass root level for the benefit and well being of the villagers. It was heartening to see the remarkable improvement in the knowledge of this part of the audience after viewing the documentary. This would enable them to take this learning back to the rural population and educate and orient them effectively. Any ADRs resulting from the treatment could thus be identified early and necessary care and attention could thus be made available to the people at the right time. Identifying and reporting of cases by the ASHA workers to the PHC’s and in turn back to healthcare professionals could be vastly improved, thus providing better and safe healthcare to the rural masses.

Patients commented that it was easy for them to understand the content and information that was shared and something that they could take back to their families, relatives and fellow villagers.

The audiovisual training module was initially developed in English with the understanding that it would be appropriate for the physicians. However, from the feedback received in the field, a need to develop the training module for physicians in Hindi, which is the local language, with technical terminologies in English was strongly expressed as this would be appropriate for physicians from PHCs as well. The training module was then reshot as per the feedback and re circulated. The physicians said that it was now easier for them to accurately understand and discuss the content of the module.
As the DVD was played on the laptop, the sound was not as loud as was needed and hence the sound of the entire movie needed to be increased so that it can be heard by a group of 20 patients and physicians without speakers. This problem was addressed when the documentary was reshoot as mentioned above.

The Kala-Azar 4 page OPD card was able to capture detailed information as compared to the earlier OPD card (which was not available at all the PHCs). However, physicians from the PHCs and RMRI commented that the OPD card is too long and it will not be filled by the physicians at the PHCs as it would add further pressure to their already burdened schedules. In view of this observation, it was decided that the OPD card would be redesigned to a Kala-Azar 2 page OPD card which would be easier to complete. This OPD card is made available at the PHCs. The Kala-Azar 4 page OPD would be used when a dedicated person is available for pharmacovigilance.

The patients could fill in the patient card correctly after viewing the video. This would give us an account of compliance if the patient is asked to fill in on a regular basis.

This documentary (DVD) has now been officially adopted for training health workers and patients under the WHO-TDR (Tropical Diseases Research) Programme for the elimination of leishmaniasis in India, Nepal and Bangladesh.

Further the plan is to test this DVD in Nepal and Bangladesh and conduct a similar study for which the dubbing of the DVD in the local language of Nepal (Nepali) and Bangladesh (Bengali) is under process.

The trailer of this video can be viewed on www.muhsnashik.com66
B. Risk Assessment

The next step after risk minimization is risk assessment. Risk assessment is the process of identifying, estimating and evaluating the nature and severity of risks associated with a product throughout its lifecycle. The goal is to better access and communicate information on the effectiveness and risks of medicines and to educate and inform patients.

Out of various methods for assessment of risks, spontaneous reporting system was selected for the study. Spontaneous reporting is a system whereby case reports of adverse drug events are voluntarily submitted by health professionals and pharmaceutical companies to the national pharmacovigilance centre. Spontaneous reporting of suspected ADRs enables medicines to be monitored throughout their lifetime.

The success or failure of any pharmacovigilance activity depends not only on the reporting of suspected adverse reactions but also on the accurate assessment of the case reports. In depth knowledge and understanding of the various fundamentals involved such as causality assessment, coding of suspected adverse drug reactions as per globally accepted dictionaries, process of data entry into ADR databases and the tools available for this entire process is extremely essential for the successful development of the pharmacovigilance programme.

As such the rigorous training imparted to me provided valuable insights in risk assessment and the importance of this step in the pharmacovigilance programme development.
C. Analysis of Pharmacovigilance data

Spontaneous reporting forms from four developing African countries were received and analyzed for causality. Overall quality of forms was fair. However, several gaps were noticed which could be strengthened to improve the quality of source data to do better analysis & causality assessment.

Quality of Pharmacovigilance Data

In most of the forms from all the counties, vital information for causality assessment was either missing or insufficiently reported. Eg: Stop date of reaction, date of change of therapy, information of concomitant medication if used etc. This reinforces the need to train and educate the ground staff who are primary contact points for efficient reporting of ADRs. A documentary based training module similar to the one developed for the WHO-TDR (Tropical Diseases Research) Programme for the “Elimination of Leishmaniasis” can be replicated for these African nations customized as per their individual requirements. Based on past experience, such a training programme could immensely improve the quality of reporting. This will then give a more accurate picture about the scenario of ADRs reported to drugs.

Quality of Spontaneous ADR reporting forms

The quality of the spontaneous ADR reporting form is vital and the key instrument for capturing complete information on adverse drug reactions. However, the ADR forms of the four nations were found to be lacking in quality and did not aid the reporters in adequately capturing all necessary information about ADRs. It was observed that ADR forms did not have space for writing information regarding rechallenge & dechallenge
tests, relevant medical history & past drug history. Of the spontaneous reporting forms of the four countries that were analyzed, forms from Tanzania and Sierra Leone had provision for capturing all the relevant information regarding ADRs, but it did not have enough space for description of the ADRs. As a result of which the reporter was forced to write in small handwriting with minimal information. It was difficult and sometimes impossible to understand what the reporter was trying to convey and crucial data could have been missed. Also the space provided for capturing suspected drug which is the most crucial part of any ADR was very less. In Tanzania only 3 suspected drugs could be captured and in Sierra Leone the space provided was so less that only a single drug could be captured with great difficulty. Except Tanzania all the other countries did not have provision for capturing pregnancy status, history of allergies and medical history. Zambia and Ghana did not have provision for capturing information on rechallenge.

Looking at the shortcomings in the ADR reporting forms of the above nations and with the knowledge that different countries have different forms, a study was conducted to analyze the suspected adverse drug reaction reporting form of different countries and assess if these forms can capture all the data regarding the adverse drug reaction.

Spontaneous adverse drug reaction reporting form is an essential component and a major tool of the pharmacovigilance system of any country. This form is a tool to collect information of ADRs which helps in establishing the causal relationship between the suspected drug and the reaction. If relevant information regarding ADR is not adequately captured then it is of no use for the regulatory authority as no conclusion can be drawn from the data. Every country has developed its own spontaneous ADR reporting form for data collection which is used by them to capture information about an adverse event. The
newsletter of WHO Pharmaceuticals has also cited the need for a generic form for spontaneous reporting of adverse drug reactions

It was observed that there is a need to harmonize the ADR reporting forms of all the countries because there is a lot of discrepancy in data captured by the existing ADR reporting forms as the design of these forms is different for different countries. The WHO receives information of the adverse events from all the countries that are members of the international drug monitoring programme. The data is collated to generate potential signals; therefore, the data received by the WHO has to be uniform and complete to draw meaningful conclusions. Each country has its own spontaneous reporting form as per the individual countries’ requirements. It was noted that there should be international guidelines and checklists for the inclusion of mandatory information needed for causality assessment for drafting and designing of spontaneous reporting form by countries. The introduction of guidelines for developing an effective spontaneous reporting form to capture complete adverse event-related information by WHO is the need of the hour.

Part 2: Testing of the Developed Programme

A. By performing retrospective analysis of adverse drug reactions in HIV/AIDS and TB co infected patients on HAART (Highly Active Anti Retroviral Therapy)

India is increasingly utilizing generic antiretroviral therapy. HAART therapy is proved to be useful to HIV patients but it is associated with different adverse drug reactions such as peripheral neuropathy, anemia, rash, lactic acidosis, Stevens Johnson syndrome etc of which the prevalence of peripheral neuropathy and anemia were observed maximum in
this study. TB co infected patients on HAART require modifications in the HAART regimens. As rifampicin reduced the concentrations of nevirapine, TB co infected patients are shifted to efavirenz based regiments. Pregnant women on efavirenz based regimen require change in the DOTS therapy also, in such cases rifampicin is substituted by rifabutin. Thus co infected patients are at a higher risk of toxicities which makes pharmacovigilance utmost necessary.

In patients with HIV/AIDS and on HAART, anemia was commonly observed in patients on zidovudine containing regimen within first month after initiation of therapy which was found similar as reported by other studies\textsuperscript{68, 69}. Nevirapine and stavudine use was identified as risk factors for development of skin reactions and peripheral neuropathy which is also reported in other studies\textsuperscript{70, 71}.

19.68% of HIV infected patients were co infected with TB. This percentage is similar to the other studies carried out in India and abroad. TB co infected patients on HAART were either put on stavudine+lamivudine+efavirenz or Zidovudine+Lamivudine+Efavirenz regiments. In HIV/TB co infected patients peripheral neuropathy was found to be the most common ADR as it is observed with both HAART and DOTS treatment regimens. More ADRs were noted in the stavudine+lamivudine+efavirenz group. As antiretroviral therapy and DOTS therapy are given in combination it is difficult to establish causality for one individual drug.

Through statistical analysis and assessment, it was observed that ADRs are higher in patients with TB co infection than with HIV alone. Also the severity of ADRs among this
group is much higher than with only HIV. Similar results have been demonstrated by other studies reinforcing the need for active pharmacovigilance surveillance.

Being a retrospective study the ADRs which were reported on the case report form were only included for analysis. ADRs observed in this study were far less than the ADRs reported in developed countries. This could be because of lack of active pharmacovigilance in India. Physicians do not report ADRs due to heavy patient load and less knowledge about the importance of pharmacovigilance. Secondly, record form used to enter patients’ data does not have proper section to write about adverse drug reactions, therefore data obtained from records was incomplete with respect to laboratory test results, outcome of dechallenge and rechallenge tests due to which maximum ADRs were categorized as possible even if they could have been probable if complete documentation was available.

ART centre now has started to issue a small notebook to patients which they have to carry with them at each and every single visit. Physicians have started noting down all symptoms and observations and most importantly ADRs experienced by the patients in this notebook, which is useful for complete analysis of the ADR. All records of ART drugs are in their generic names which makes impossible to correlate between ADR and the specific brand or product. Also ART therapy is available in a combination of three drugs thus it becomes more difficult to establish causal relationship of ADR with one specific drug. All reported ADRs should be documented properly to generate safety data of ART drugs in the country.
HIV and HIV/TB patients on stavudine based regimen require intensive monitoring for ADRs. Active pharmacovigilance programme should be implemented and awareness should be created among physicians about reporting any suspected adverse drug reaction so that unreported ADR and unknown risk factors can be identified.

Analysis of HIV/TB research data is crucial for generating evidence and promoting collaborative action between the HIV and TB control programmes. Also, screening for TB should be mandatory before beginning anti retroviral therapy which will help plan the course of treatment.

B. By conducting intensive adverse drug reaction monitoring in Psychiatry

Psychotropic drugs are plentiful in number and their use is increasing day by day. These drugs are capable of causing a number of adverse drug reactions (ADR)\textsuperscript{72, 73}. Pharmacovigilance in psychiatry units play a vital role in detecting ADRs and alerting physicians to the possibility and circumstances of such events, thereby protecting the user population from avoidable harm\textsuperscript{74}. In India, Pharmacovigilance activities are still in nascent stage and there are few reports available on the ADR profile of medicines in general and psychotropic agents in particular. Not many studies have been carried out in the Indian populations to aid, inform and educate the medical community about the nature of adverse drug reactions.

The present study has attempted to profile suspected ADRs to psychotropic drugs in the psychiatry OPD setting in the Indian context. In contrast to reports of ADR profiles of individual drugs, there is a dearth of Pharmacovigilance profiling of psychotropic agents.
in general, not only in India but also worldwide. A Brazilian study, conducted in 2001, analyzed 219 notifications of suspected ADRs of psychoactive medicaments and incriminated antidepressants as the commonest group responsible for ADRs, followed by antipsychotics. A Bulgarian study reported that the ADR frequency of individual psychotropic drugs studied is less than 1%. A knowledge, attitude and practice based study conducted in Norway found that ADRs can be prevented by collecting reliable information about their frequencies and possible risk factors.

This study is based on active surveillance rather than spontaneous reporting. It was observed that 253 patients developed 348 ADRs. The average strength of the OPD was around 86 patients. Schizophrenia was the commonest clinical diagnosis which was followed by depression and bipolar disorder.

Maximum ADRs observed were of extra pyramidal reactions. The number of these ADRs was high probably because these were majorly looked for by the treating physicians.

Tremors were the commonest type of ADRs which was seen during the study period which was followed by tardive dyskinesia, weight gain, dystonia and akathisia. Haloperidol is reported to cause tremors, tardive dyskinesia and akathisia and olanzepine is associated with weight gain. The high number of these ADRs can be attributed to the fact that haloperidol and olanzepine are the most widely prescribed drugs in the hospital setting. Ammenhoroea cases observed in the female patients were suspected to be caused because of risperidone.

Haloperidol followed by olanzepine were frequently prescribed in our setting, as they are dispensed free of cost from the hospital pharmacy. Although several new psychotropic
drugs have been introduced in the Indian pharmaceutical market over the last few years (e.g., reboxetine), they were not included in our study because they are relatively expensive and not dispensed from the hospital pharmacy. Hence, they were seldom prescribed in our setting a public hospital catering mostly to economically weaker sections of society.

Other ADRs like dryness of mouth, constipation which were not as disturbing (to major extent) were not seriously referred as they were not given much weightage by the treating physicians.

The causality assessment revealed that there were no “Definite” cases since cases where dechallenge was done, rechallenge was not attempted with the offending drug. This is in contrast to the Brazilian study where 24 cases were found to be “definite” after rechallenge was attempted. The suspected ADRs were mostly of mild to moderate severity but no severe cases were observed. Only two percent cases were found to be preventable as per the Schmoch & Thornton scale and two percent cases were found to be of “Serious” nature as per the WHO criteria for seriousness assessment.

This study had limitations. Patients with confirmed diagnosis of AEs by the treating physicians and referred were only included in the study. Being an OPD based study, it is likely that some ADRs could have been missed that were transient or too mild to have inconvenienced the patient to an extent sufficient to report to the doctor on the next hospital visit. Although routine hematological and clinical chemistry (e.g., blood sugar, lipids) reports were available, tests like ECG screening of patients for QT interval
prolongation or blood sampling to determine serum prolactin concentration could not generally be ordered.

The Psychiatry department had not been following any pharmacovigilance method for reporting ADRs till the time the study was conducted. Only serious ADRs had a chance of being detected and reported while the others were not attempted to be tracked or captured. Through active Pharmacovigilance method which was carried out, the ADRs were recorded and assessed in a systematic manner, which would have otherwise gone unreported.

It was also notably observed that the frequency of reporting ADRs increased over the study period as the physicians became more aware of the advantages of reporting and the information that was to be gained by analysis of the ADR data recorded. Such analysis and discussions will enable the physicians to take a more informed decision while prescribing certain drugs depending on the patients’ previous history, demographics and the absolute need for the drug, assessing the risk-benefit ratio.

Several physicians suggested that training or an orientation programme should be carried out for educating them on the process of reporting AEs. As compliance with therapy is a major issue in psychiatric patients, these programs should be extended to the patients as well to create awareness. Use of visual aids for training and awareness programs could prove to be an effective medium for increasing the knowledge of physicians and patients. This will also act as a mean for educating the interns on how to look for AEs as they cater to the old patients who come for renewal of prescriptions.
Constant vigil in detecting ADRs and subsequent dose adjustments can make therapy with psychotropic drugs safer and more effective. Patients could be forewarned about possible ADRs thus preventing them from discontinuation of treatment.

This study offers a representative idea of the ADR profile of psychotropic drugs likely to be encountered in ambulatory patients in an Indian public hospital. Findings of the study provide insight into the type and nature of ADRs in the Indian population. It has encouraged the Psychiatry department to stress the importance of Adverse Drug Monitoring to the physicians and imbibe this as a part of their job.

More studies like this could provide valuable information about drugs which cause large number of ADRs yet continue to be widely prescribed in government health care centers due to lack of evidence to conduct further investigation of some of these drugs.

A psychotropic drug ADR database built up on the basis of such studies conducted across multiple centers, through active collaboration of psychiatrists and pharmacologists, can be a worthy long-term goal in the Indian context. Such a database can provide early warning signals of drug-reaction links if kept under active scrutiny.