OVERALL DISCUSSION

Pharmacovigilance is defined as “The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicines-related problems”. Not everything is known about a medicine when it receives its license for marketing. At this point, most medicines will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals. The merits of a new drug, balancing its beneficial and its untoward effects become established only after sufficient experience has been gained from its use in real practice. For good reason, therefore, it is essential that new and medically still evolving treatments are monitored for their effectiveness and safety under real-life conditions post release. More information is generally needed about use in specific population groups, notably children, pregnant women and the elderly, and about the efficacy and safety of chronic use, especially in combination with other medicines.

It was not until the disaster caused by the drug thalidomide in 1961 which caused major birth defects in an estimated 10,000 children in the countries in which it was widely used in pregnant women, that the first systematic international efforts were initiated to address drug safety issues. As a means of pooling existing data on ADRs, WHO’s Programme for International Drug Monitoring was started. Initially a pilot project in 10 countries with established national reporting systems for ADRs was launched, the network has since expanded and currently, 86 countries participate in the programme, which is coordinated by WHO together with its collaborating centre in Uppsala, Sweden The collaborating
centre is responsible for maintaining the global ADR database, Vigibase. At present the database contains more than three million ADR reports.

While major advancements in the area of Pharmacovigilance have taken place in the developed western countries, not much has been achieved in India. Healthcare professionals and healthcare workers are unaware of the importance of the Pharmacovigilance which is indicated by the fewer number of studies that are being carried out in this area, resulting in incomplete and insufficient data about possible adverse drug reactions in Indian population. Indian regulatory agencies have to depend on information and experience of drugs in other markets to assess risks and benefits of drugs made available in Indian markets. Information obtained in one country (e.g. the country of origin of the drug) may not be relevant to other parts of the world, where circumstances may differ. Data derived from within the country or region does have greater relevance and educational value for national regulatory decision-making, thereby stressing the importance of developing an adequately designed Pharmacovigilance system in India.

The objectives of the present study were to 1) Develop a Pharmacovigilance programme which involves risk minimization, risk assessment and analysis of Pharmacovigilance data and 2) To test the developed programme by A) Performing retrospective analysis of adverse drug reactions in HIV/AIDS and TB co infected patients on HAART (Highly Active Anti Retroviral Therapy) and B) Conducting intensive adverse drug reaction monitoring in Psychiatry.
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. The video training method for Pharmacovigilance was thought to be better than the other methods. It 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 with the training module was field tested at the Rajendra Memorial Research Institute of Medical Sciences (RMRI), Patna and Public Health Centers (PHCs) in 3 districts of Bihar. In order to evaluate the impact of the training module on the understanding of the physicians, health workers and patients about the appropriate use of miltefosine, a new oral drug for Visceral Leishmaniasis (KalazAzar), a survey questionnaire was developed and administered before and after viewing the documentary. 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. This group showed remarkable improvement after viewing the documentary. This would enable them to take this learning back to the rural population and educate and orient them effectively. The 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.

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 medicine 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. 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 and the tools available for this entire process is extremely essential for the successful development of the Pharmacovigilance programme.

Training was imparted by WHO officials for causality assessment and data entry into Vigiflow. It is a web-based Individual Case Safety Report (ICSR) management system
that is specially designed for use by national centers in the WHO Programme for International Drug Monitoring. At the end of the training program, certification was obtained from WHO’s Uppsala monitoring centre, Sweden for “Data entry into Vigiflow”. The rigorous training imparted provided valuable insights in risk assessment and the importance of this step in the Pharmacovigilance programme development.

**Analysis of Pharmacovigilance Data** was then carried out through causality assessment of spontaneous reports from 4 African countries. These reports were further entered into the Vigiflow and individual countries’ national databases. 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.

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 is 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.

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. 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. Every country had developed its own spontaneous ADR reporting form for data collection which is used by them to capture information about an adverse event. 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 program. 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. 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.

Once the Pharmacovigilance programme was successfully developed, the next step involved was **Testing of the developed Pharmacovigilance programme** and was carried out in 2 parts. First, a retrospective study was carried out to find out the ADRs reported in HIV/AIDS and TB co infected patients on HAART (Highly Active Anti Retroviral Therapy) at the King Edward VII Memorial (KEM) Hospital a tertiary referral center in Mumbai, India. 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, Steven’s-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.

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.

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

For the second part in testing of the developed Pharmacovigilance programme, a prospective observational study was conducted at the Psychiatry OPD (Out Patient Department) of King Edward VII Memorial (KEM) Hospital. Psychiatry department was selected as there are many adverse drug reactions reported to psychotropic drugs which affect the quality of life and compliance to treatment, and also very few studies are carried out in the Indian population to study the nature and type of these ADRs.

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 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 they were seldom prescribed in our setting – a public hospital catering mostly to economically weaker sections of society.

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 patient’s previous history, demographics and the absolute need for the drug, assessing the risk-benefit ratio.

Several physicians suggested that training or an orientation program 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 ADR’s thus preventing them from discontinuation of treatment.

The present 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.

The present study has highlighted the fact that 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 and rational therapy, and on a population basis, will help to ensure the acceptance and effectiveness of public health programmes. In spite of this, it is not widely practiced in Indian hospitals. The idea that Pharmacovigilance program can be set up 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.