5. MATERIALS AND METHODS

This study was carried out in a tertiary care teaching hospital located in South India, over a period of three years from April 1, 2012 to March 30, 2015. The study assessed the pattern, severity, preventability, predictors and direct cost associated with the management of ADRs in patients with mental disorders. Also, the study determined the prevalence and pattern of ADI in psychiatric practice.

5.1 Study Setting

This study was conducted in the psychiatric department of Jagadguru Sri Shivarathreeshwara Hospital (JSSH), Mysore. It is a 1800 bed multi-speciality tertiary care teaching hospital. The department of psychiatry comprises of two general psychiatric units and manpower includes six psychiatrists, two psychologist, one psychiatric social worker, 11 psychiatric postgraduate students and five psychiatric nurses. To the holistic management of patient, department is using the latest developments in the field, and being a tertiary care hospital, cases from other places located in and around Mysore district are referred to the department. There are 30 beds in the general psychiatric ward and it provides the patient treatment to approximately 5600 patients per year both in inpatients and outpatients setting.

5.2 Study Design

This is a prospective observational study and adopted both spontaneous reporting and active surveillance pharmacovigilance methodology.
5.3 Study Period

The study was conducted over a period of 36 months from April 2012 to March 2015.

5.4 Ethics Committee Approval

The study protocol was reviewed and approved by Institutional Human Ethical Committee of Jagadguru Sri Shivarathreeshwara College of Pharmacy, Mysore, [Appendix I] and also administrative approval was obtained from the JSS hospital authority prior to the commencement of study.

5.5 Study Population

The study randomly reviewed all the patients visited to the department of psychiatry, while exempting those who were treated in consultation liaison with the psychiatric department for the want of complete medical information of the patients.

5.5.1 Study criteria

5.5.1.1 Inclusion Criteria

- Patients presented with psychiatric illness as diagnosed by ICD-10
- Patients of any age and gender
- Patients who were either admitted to psychiatry ward or treated on outpatient basis
- Patients who were receiving at least single psychotropic agent
5.5.1.2 Exclusion Criteria

- Aggressive and violent patients
- Psychiatric patients who were treated in other medical departments
- Psychiatric patients receiving medicines other than allopathic
- Psychiatric patients who experienced adverse event to vaccines, blood and/or blood products
- Adverse event to overdose/poisoning/drug abuse and dependence

5.6 Source of Data

Medical records including clinicians’ admission notes, discharge summaries of previous hospitalizations (available with the patients or in the out-patient file), reference note from other clinicians and discussion with the patient or their care takers at the time of patients’ inclusion were considered as sources of past medical and medication history for both inpatients and outpatients. Clinicians’ notes, discussion with the clinicians/medical postgraduate (PG) students were the important sources of information for current medical conditions. To gather the information regarding medication use during hospital stay, treatment charts and nurses’ notes were reviewed throughout the patient’s stay in hospital. While in case of outpatients, patients OPD cards, prescriptions and bills produced by the pharmacy or the empty strip of the medication carried by the patient or the care taker were considered as sources of information for medication details. Hospital bills and pharmacy bills were the source documents to determine the cost of hospitalization and cost associated with the management of ADRs. Information required for the assessment of ADR was obtained from standard drug information resources.
5.7 Methods

5.7.1 Definitions of terminology

For the purpose of this study, following definitions of terminology were adopted.

5.7.1.1 Adverse Event/Adverse Experience (AE)

An adverse outcome that occurs during treatment with a pharmaceutical product but which does not necessarily have a causal relation to the treatment.207

5.7.1.2 Adverse Drug Reaction (ADR)

The World Health Organization (WHO) definition of ADR was adopted. WHO defines an ADR ‘Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function’.226

5.7.1.3 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening is considered as a serious adverse event as per International Conference on Harmonisation-Good Clinical Practice (ICH- GCP) guidelines.227

5.7.1.4 Long-term ADR

An ADR that occurs, after 6 months of initiation of the drug is considered as long-term ADR.228
5.7.1.5 **Short-term ADR**

An ADR that occur within 6 months of initiation of the drug is considered as short-term ADR.\(^{228}\)

5.7.1.6 **Drug-Drug Interaction (DDI)**

A DDI is defined as the concomitant use of two different drugs (more than 1 days overlap use) that interact in such a way that the effectiveness or toxicity of one or both could be altered and will lead to clinically significant interaction effects.\(^{229,30}\)

5.7.1.7 **Adverse Drug Interaction (ADI)**

When a drug-drug interaction is of clinical concern or leads to an undesired effects and the suspected drug was interacting agent/index drug in the DDI then it is considered as an ADI.\(^{33}\)

5.7.1.8 **Medication Adherence**

WHO definition “The extent to which the patient follows medical instructions” was adopted for medication adherence in this study.\(^{121}\)

5.7.2 **Study procedure**

5.7.2.1 **Design of Data Collection Form**

Suitable data collection, documentation and assessment forms were developed for documenting the patient informations.
5.7.2.1.a Development of patient appraisal form

‘Patient appraisal form’ was designed separately for inpatients (Appendix II) and outpatients (Appendix III) to document all the required information about the study patients. The appraisal form consists of patient information including demographic details, patient visit details, diagnosis, complete dosing regimen of current medications and medication on previous visit/admission and also follow up information.

5.7.2.1.b Design of patient data collection form

A suitable ‘patient data collection’ form for both inpatients (Appendix IV) and outpatients (Appendix V) was designed separately for collecting complete information about patients who develop ADRs. In the data collection form, provisions were made to document the information regarding patient demography, medical and medication history, reason for admission, diagnosis, medications used during the hospital stay, description of the suspected ADE, details of laboratory investigations, duration of stay in the ward, management and outcome of the suspected ADE. Also it included information pertaining to the ADI like index and interacting drug, interaction effect, mechanism, severity, onset and clinical management. Self reported medication adherence was documented in the data collection form by administering the Medication Adherence Rating Scale (MARS).230

5.7.2.1. c Preparation of ADR assessment form

An ADR assessment form [Appendix VI] was designed to document the outcome of ADR assessment. The designed ADR assessment form consists of details of the suspected adverse reactions including brief description of the reaction, nature of the
reaction, date of onset of the reaction, treatment and outcome of the reaction; complete dosing regimen of the suspected drug(s). Also, it included the various parameters/criteria’s pertaining to causality categories, severity ratings, predictability and preventability based on different standard scales that were adopted in the assessment of ADR. Also it was designed to incorporate other required details pertaining to ADR and ADI such as type of ADR, mode of reporting, time taken for ADR detection and cost associated with the management of ADR.

5.7.2.2 Meetings with the Psychiatry Health Care Team

At the time of initiating the study, personal meetings were held with psychiatry team and were briefed about the objectives and operational modalities of the study and were encouraged to notify any suspected ADRs observed in the patients who visited or admitted in the psychiatric department. Throughout the study period, all the psychiatrists, postgraduate medical students and nursing staff were encouraged to notify the suspected ADRs.

5.7.2.3 Constitution of Independent Clinical Panel

An independent clinical panel consisting of two consultant psychiatrists, a medical doctor, a clinical pharmacist and a postgraduate medical student was constituted. The five-member panel reviewed and assessed the clinical significance of pDDI identified by the study pharmacist on weekly basis. The assessment was based on a review of the individual case, and all the information pertaining to the suspected ADR and pDDI were reviewed to arrive the decision based on consensus method. The decision by the panel on the basis of their knowledge, expertise and referral of appropriate literature.
5.7.3 Data collection

This prospective study adopted both spontaneous reporting and active surveillance pharmacovigilance methodology simultaneously.

5.7.3.1 Adverse Drug Reaction

5.7.3.1.a Spontaneous reporting

Adverse drug reaction reports were accepted from all the healthcare professionals of psychiatric department irrespective of their status and types of services offered. A predesigned suitable “ADR notification form” [Appendix VII] was made available at both outpatient and inpatient unit of the psychiatric department. This was prepared based on a format similar to the national pharmacovigilance program of India (PVPI). This notification form contained only the basic and essential information such as patient demographic details, information about the suspected medication, description of event, date and signature of the reporter. Psychiatrists, nurses and other health care professionals were asked to fill in the notification form, when they encountered suspected ADRs. Apart from notification form, other modes of reporting such as telephonic reporting, direct access, referral of patients and personal meeting were adopted to ease the reporting of “suspected” ADRs. The reporter was not required to prove cause and effect prior to the reporting of “suspected” adverse drug reaction. Once the suspected ADR was reported, patients’ medical records were reviewed and also patients and or healthcare professionals were interviewed as needed to collect all the necessary and relevant data pertaining to the “suspected” ADR.
5.7.3.1.b Intensive monitoring

All the patients admitted to the psychiatric ward were intensively monitored on daily basis from the day of admission to till the day of discharge. While, the out patients were randomly reviewed on their visits to the outpatient department (OPD) to detect any new symptoms that might be associated with the use of medicine. Any adverse event noted by the study pharmacist was brought to the notice of the concerned psychiatrist and the adverse outcome was labeled as adverse drug reaction only after discussing with the consultant. In case of any difference of opinion with respect to the suspected reaction, treating psychiatrist’s opinion was considered as final. All the information required for the assessment of identified ADRs was gathered using various patient information sources and standard drug information resources. All the collected data such as patients’ details, medication details, event details and other relevant data were documented in a suitably designed data collection forms [Appendix II- VI].

5.7.3.2 Adverse Drug Interaction (ADI)

Once the ADR was reported or identified, the patient and/or care taker was interviewed regarding their medication use history including the list of prescription drugs and self medication up to 3 months prior to the visit/admission. All the information pertaining to the medication history such as start date and end date of therapy, name of the medication were also documented based on the available information recourses. Also questions such as ‘did you suffer from any other illness during this period’? or did you actually take this drug (documented in the chart/present with the patient) were added to help clarify the patient and to address the potential recall bias. In addition, physical verification of all the medications were
carried out to check the consistency of the self reported information. After identifying all the drugs administered concomitantly potential drug-drug interactions (pDDI) were identified using the online version of computerized interaction detection systems such as Micromedex, Medscape, Drugs.com and Stockley’s drug interaction textbook.

In the subsequent steps, pDDIs resulted in ADR was further investigated by the independent panel. The reported ADR was categorized as ADI, when the suspected drug is involved in the DDI and the ADR was corresponding to the description of the interaction effect described in drug interaction programs or textbook. The drugs involved in the interaction were categorized as Index drug (The object drug whose effect resulted in an ADR) and Interacting agent (The perpetrator drug which altered the pharmacokinetics or pharmacodynamic of the index drug which resulted in an ADR). Identified ADI was assessed for its mechanism, severity and onset were documented.

5.7.4 Follow up

All the patients were followed regularly during their onsite visits for identification and documentation of both short-term and long-term ADRs. The follow up process consisted of patents interview and chart review. ADRs and pDDI related ADRs were identified using both objective markers (eg. weight & blood pressure measures and laboratory results) and subjective markers (eg. headache, rash and nausea). In addition, the patients were instructed to contact the study pharmacist (available in the psychiatric department), if any new symptoms occurred or any new drug was initiated during the follow up period. Also, the treating psychiatrists were informed to refer patients, if an ADR was suspected. All the information collected during the follow up period was also documented in a suitably designed data collection forms [Appendix II- VI].
5.7.5 Assessment of ADR/ADI reports

5.7.5.1 Classification of Adverse Drug Reaction

Each of the reported ADRs was classified as per the Royers\textsuperscript{231} classification into either Type A (Augmented), Type B (Bizarre), Type C (Chronic) or Type D (Delayed).

5.7.5.2 Short-term and Long-term ADRs

All the reported ADRs were categorized into short-term and long-term ADRs based on the onset of the reaction.

5.7.5.3 Medications Implicated in ADRs

Drugs that implicated in adverse reaction were coded using the WHO Anatomical, Therapeutic and Chemical (ATC) classification.\textsuperscript{232} The WHO-ATC assigns a six character alpha numerical code for each drug which identify the anatomical main group, therapeutic, pharmacological and chemical sub group and chemical substance of the drug.

5.7.5.4 Organ Systems Affected due to ADRs

The organ system affected due to ADR, were determined by using the WHO Adverse Reaction Terminologies (ART)\textsuperscript{233} This terminology is a hierarchical, and link system or organ classes to three types of terms: broad “high-level” terms; more specific and disease related or symptom related “preferred” terms; and finally the frequently reported alternative “included” terms and true synonyms. All the reported ADRs were coded by using ‘preferred’ term and were assigned with the respective system organ class to identify the organ system affected due to ADRs.
5.7.5.5 Causality Assessment of ADRs

When an adverse event is identified/reported, causal relationship between the reported adverse reaction and suspected drug was established by using WHO probability scale and Naranjo’s algorithm (Appendix VIII & IX). The causality of reported reactions was categorized into ‘certain’, ‘probable’, ‘possible’, ‘unassessable/unclassifiable’, ‘unlikely’, and ‘conditional/unclassified’ by using WHO probability scale and by using Naranjo’s scale causality of the reported reaction were categorized into ‘definite’, ‘probable’, ‘possible’ and ‘unlikely’.

5.7.5.6 Assessment of Severity of ADRs

Severity of the reported ADR was categorized as ‘mild’, ‘moderate’ and ‘severe’ based on the severity level (Level 1 to Level 7) as assigned in the modified Hartwig & Seigel scale (Appendix X).

5.7.5.7 Assessment of Magnitude of Individual ADRs & Its Interference with Patient Daily Performance

Magnitude of the individual symptoms was presented as ‘mild’, ‘moderate’ and ‘severe’ by using Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale (Appendix XI). The scoring sheet includes 48 items clustered into four subgroups: psychic, neurological, autonomic and other side effects. A global assessment of interference by the existing side effects with patients, daily performance was made by the patient and were categorized ranging from 0 (not or doubtfully present) to 3 (side effects that interfere markedly with the patient's performance).
5.7.5.8 Assessment of Seriousness of ADRs

The seriousness of the adverse drug reaction was categorized into ‘serious’ and ‘non-serious’ by adopting the criteria of International Conference on Harmonization Tripartite Guidelines (ICH - E2A Guidelines).

5.7.5.9 Assessment of Predictability of ADRs

The predictability of the reported ADRs was assessed by using developed criterion (Appendix XII) and was categorized as ‘predictable’ or ‘not predictable’ based on the previous exposure of the medication and incidence rate of reported adverse drug reaction.

5.7.5.10 Assessment of Preventability of ADRs

All reported ADRs were evaluated for preventability by using the modified Shumock and Thornton criteria which categorizes the reactions into ‘definitely preventable’, ‘probably preventable’ and ‘not preventable’ (Appendix XIII).

5.7.5.11 Evaluation of Extra Pyramidal Side Effects

Severity rating of the extra pyramidal symptoms such as parkinsonism, dystonia, akathisia and tardive dyskinesia was done by using Extra Pyramidal Symptoms Rating Scale (ESRS) (Appendix XIV). It is a 28-item scale for the comprehensive measurement of extra-pyramidal symptoms through a combination of a clinical interview, as well as a motor examination. Each item is rated from 0(absent) to 8 (extremely severe).
55.7.5.12 Predictors of ADRs

Different variables that were subjected to testing include age, gender, number of diseases, number of medications, drug-drug interactions, and comorbid medical conditions. Predictors of ADRs were determined by using multivariate regression analysis.

5.7.5.13 Direct Cost Associated with Management of ADRs

Direct cost associated with the management of ADRs was calculated by considering the cost of medications, medical devices, bed charges, laboratory investigations charges, consultation fee and other relevant charges. (e.g., cost of registration as an in-patient, procedure charges etc).

5.7.5.14 Causality Assessment of Adverse Drug Interaction (ADI)

The causal relationship between a potential drug-drug interaction and an event was assessed by using Drug Interaction Probability Scale (DIPS) (Appendix XV). Based on this scale, each of the ADIs were classified into any one of the categories as ‘highly probable’, ‘probable’, ‘possible’ and ‘doubtful’.

5.7.5.15 Severity of ADI

The severity of the pDDIs that led to ADIs was classified into contraindicated, major, moderate or minor based on the following criteria.

Contraindicated – The drug combination is contraindicated for concurrent use.

Major – If there is risk of death and/or medical intervention is required to prevent or minimize serious negative outcomes.
Moderate – The effect of interaction can deteriorate patient’s condition and may require alteration of therapy.

Minor – Little effects are produced that do not deteriorate patient’s condition and may require alteration of therapy.

5.7.5.16 Onset of ADI

The onset of ADI was classified into either rapid or delayed, based on the criteria as follows:

Rapid – The effect of interaction that occurred within 24 hours of drug administration.

Delayed – The effect of a interaction that occurred after 24 hours, that is, days to weeks of administration of interacting combinations.

5.7.5.17 Medication Adherence

The Medication Adherence Rating Scale (MARS)²³⁰ (Appendix XVI) was used to assess the level of medication adherence in study patients. The scale includes 10 items and examines adherence behaviors and attitude toward medication use during past week with relatively simple scoring. Scoring less than 60% was considered as non-adherence to the medications.

5.7.6 Documentation

5.7.6.1 Paper Based Documentation

After assessing the suspected ADR/ADIs, all the information were documented in the suspected ADR assessment forms.
5.7.6.2 Computerized Documentation

Immediately after the assessment, all the information documented in the appraisal form, data collection form and suspected ADR assessment form were entered into a suitably designed Microsoft Access database (Appendix XVII) for easy storage, retrieval and analysis. To check the quality of the documentation and minimize the transcription errors, 20% of forms in the Microsoft database were reviewed against paper documentation for consistency of the information.

5.8 Result Analysis

All the collected data were subjected to analysis to determine the demography of the patients and the medication usage. The data was subjected to analysis to determine the prevalence, drugs implicated, organ system affected, direct cost associated with the management and risk factors for development of short and long term ADRs. Also, to determine the prevalence ADI.

5.8.1 Patient characteristics

5.8.1.1 Gender

Patients were grouped into male and female and their respective percentage proportions were calculated.

5.8.1.2 Age

Median age of the study population was calculated. Patients age was subclassified into different age groups with a difference of 10 years between the groups and their percentage proportion was calculated.
5.8.1.3 **Category**

Patients were categorized into inpatients and outpatients based on their type of visit and their respective percentage proportions were calculated.

5.8.1.4 **Number of Medications Used**

Patients were categorized based on the number of medication received by them and their respective percentage proportions were calculated.

5.8.1.5 **Diagnosis**

Patients were categorized based on their diagnosis as per chapter 5 of ICD10 (F0-F99) and their respective percentages proportions were calculated.

5.8.1.6 **Co morbid Conditions**

Patients co-morbid conditions were categorized as absent or present and their percentage values were calculated.

5.8.1.7 **History of Allergy to Medications**

Based on history of allergy to medications, patients were grouped into two groups ‘present’ and ‘absent’ and the data was presented as percentage value.

5.8.1.8 **Socioeconomic Status**

Socioeconomic status of all the study patients was determined according to Kuppuswamy’s Socio-Economic Status Scale and their respective percentages values were calculated.
5.8.1.9 Past Psychiatric Illness

Based on history of previous mental disorders patients were divided as ‘present’ and ‘absent’ and data was presented as percentage values.

5.8.1.10 Family Structure

Based on family structure, patients were grouped as ‘nuclear’, ‘joint’ and ‘living alone’ and their percentage values were calculated.

5.8.1.11 Medication Adherence

The status of medication adherence of the patients were categorized as adherent and non adherent based on the MARS score and their respective percentage values were calculated.

5.8.1.12 Medication Management

Medications managed by the patients were categorized into self and care givers and the percentage values were calculated.

5.8.1.13 Social Habits

Social habits of the study patients were categorized as alcoholic, smoker, alcoholic and smoker, substance abuse and nil and their percentage values were calculated.

5.8.1.14 Length of Hospital Stay

The length of hospital stay was calculated considering the duration between day of admission to the day of discharge/transfer to other ward and their respective percentage values were calculated.
5.8.2 Adverse drug reactions

5.8.2.1 Prevalence of ADRs

The overall prevalence of ADRs was determined by taking the ratio of total number of patients who experienced ADRs to the total number of patients included in the study. Also prevalence was determined separately for both inpatients and out patients.

5.8.2.2 Prevalence of ADRs Based on Patient Characteristics

Prevalence of ADRs based on specific characteristics of patients was calculated by considering number of patients experienced ADRs with a specific characteristic in relation to total number of study patients with that particular characteristic.

5.8.2.3 Medications Implicated in ADRs

Anatomical and therapeutic classes of medications implicated in ADRs were determined. Individual medications implicated in ADRs were grouped under respective therapeutic classes. Numbers of ADRs in each medication was implicated was determined. ADRs for various therapeutic classes of medications were determined and presented with their numbers.

5.8.2.4 Prevalence of ADRs to Medications Implicated in ADRs

The prevalence of ADRs to medications implicated in ADRs was calculated by considering number of patients experienced ADRs to a specific medication / class of medications in relation to total number of study patients who received that particular medication / class of medications.
5.8.2.5 Organ System Affected due to ADRs

Number of ADRs in various system organ classes of WHO ART classification were determined and their respective percentages were calculated.

5.8.2.6 Causality of ADRs

ADRs were grouped into various causality categories based on the outcome of assessment tool used and were presented as percentage values.

5.8.2.7 Severity of ADRs

Based on the outcome of severity assessment scale ADRs were grouped into various severity category and their percentage values were calculated.

5.8.2.8 Preventability of ADRs

ADRs were grouped into various preventability categories and their respective percentages were calculated.

5.8.2.9 Predictability of ADRs

ADRs were grouped into predictable and not predictable categories and their percentage were values calculated.

5.8.2.10 Interference ADRs to Patient's Daily Performance

Interference of ADRs to patients daily performance grouped into 0-3 and was presented by percentage values.
5.8.2.11 Assessment of Seriousness

The seriousness of the adverse reaction were categorized into ‘serious’ and ‘non serious’ and data were presented as percentage values.

5.8.2.12 Short and Long- term ADRs

Based on the time of onset, ADRs were grouped into short-term and long-term ADRs and their percentage values were calculated.

5.8.2.13 Predictors of Short & Long- term ADRs

Predictors of ADRs were determined at a p value <0.05 by investigating the effects of age, gender, number of diseases, number of medications and drug-drug interaction present in the study patient by using the multivariate regression analysis.

5.8.2.14 Direct Cost Associated with the Management of ADRs

Costs of medications, bed charges, laboratory investigations charges, consultation fee and other relevant charges involved in the management of ADRs were determined and their median costs and percentage were calculated in INR.

5.8.2.15 Comparison Between Patients Who Did and Did not Experience ADRs

Characteristics of patients who did and did not experience ADRs were compared using Pearson Chi Square tests.
5.8.3 Adverse drug interactions

5.8.3.1 Prevalence of ADIs

The overall prevalence of ADIs was determined by taking the ratio of total number of patients who experienced ADIs to the total number study patients. Also prevalence of ADIs was calculated based on DDI and ADR by considering number of patients experienced ADIs to the total number of DDI and ADRs respectively.

5.8.3.2 Incidence of ADIs based on Patient Characteristics

Prevalence of ADIs based on specific characteristic was calculated by considering number of patients experienced ADIs with a specific characteristic in relation to total number of study patients with DDI with that particular characteristic.

5.8.3.3 Causality of ADIs

The ADIs were grouped into various causality categories based on the outcome of assessment and the tool used for causality assessment and their respective percentage values were calculated.

5.8.3.4 Drug Combination Involved in ADIs

The drug combination involved of interaction, there intercalation effects and mechanism involved in each interaction were determined.

5.8.3.5 Type of ADI

The DDIs which led to ADIs were classified as ‘pharmacokinetic’ and ‘pharmacodynamic’ and their percentage values were calculated.
5.8.3.6 Onset of ADI

Based on the time of onset, ADIs was classified into either rapid or delayed and their percentage values were collected.

5.8.3.7 Management of ADI

Based on the fate of the interacting/index drug, the management of ADI was grouped into two and their percentage frequency was calculated.

5.8.3.8 Predictors of ADI

Predictors of ADIs were determined at a p value <0.05 by investigating the effects of age, gender, number of diseases and number of medications present in the study patient by using the multivariate regression analysis.

5.8.4 Statistical analysis

Predictors of each of short-term and long-term ADRs and ADI were determined at a p value <0.05 by investigating the effect of age, gender, co morbid medical condition, type of patients, allergic condition, medication adherence, total number of drugs prescribed and pDDI. Multivariate regression analysis was used to evaluate the influence of these predictors on development of ADRs. The demographic characters of the patients with and without ADRs were compared using Pearson Chi square test. Also the predictors of ADRs for inpatients and outpatients were determined at a p value <0.05 by multivariate regression analysis.

All the statistical analysis were performed by using Statistical Package for Social Sciences (SPSS) V21.0 software.