1. INTRODUCTION

Mental health has been hidden behind a curtain of stigma and discrimination for too long. The magnitude, suffering and burden in terms of disability and costs for individuals, families and societies are staggering. Mental health disorders are among the most common health conditions, directly affecting about a quarter of the population in any one year. According to the World Health Organization (WHO), depression will be the second leading cause of global burden of disease by the year 2020.

Before the introduction of antipsychotic medications, the treatment of mental illness consisted of institutionalization, restraint, and sedation. There observed a revolutionary developments in the management of mental illness after the introduction of the first effective psychotropic drugs: chlorpromazine, tricyclic antidepressants (TCAs) and non-selective monoamine oxidase inhibitors (MAOIs) in the early 1950s. In the beginning psychiatrists in the United States (US) were reluctant to accept the idea of treating mentally ill patients with a chemical substance. After several years of intense debate and clinical trials reported in American medical journals, chlorpromazine and related neuroleptics gained acceptance for the treatment of mental illness and it became the world’s most prescribed tranquilizer in 1960s.

Later, the introduction of first generation neuroleptic (later called antipsychotics) prompted large changes in the field of psychiatry, leading to a medical and pharmacological understanding of mental illness. The discovery of antipsychotic medication as a useful treatment for mental disorders was followed by the identification of adverse reactions, particularly extrapyramidal symptoms (EPS).
The correlation between the development of extrapyramidal symptoms and the improvement of psychotic symptoms led to the idea that side-effects were unavoidable. Later it was considered that the presence of minimal extrapyramidal symptom was the evidences of therapeutic improvement, while an excess of such effects was associated with less improvement or with deterioration.\textsuperscript{9,10}

In the early 1990s new classes of antidepressants [selective serotonin reuptake inhibitors (SSRI), serotonin nor adrenalin reuptake inhibitors (SNRIs)] and second generation antipsychotics (SGAs) were introduced into the market. With the advent of these new treatment options, entirely new concerns regarding different patterns of adverse drug reactions and drug interactions have arised.\textsuperscript{11,12} Although the prescribers of these agents have less familiarity with the safety profiles of these drugs, the new agents that have achieved significant and rapid uptake in the recent time and are widely prescribed.\textsuperscript{4-6} Therefore, it became important to accurately assess and quantify the amount of adverse effects.

Patients with mental illness suffers from increased rates of multiple medical problems, due to their lifestyle (high smoking prevalence, high-fat diet), inherent neglect of personal care, and barriers to treatment of physical illness.\textsuperscript{13,14} A further important contributor to adverse health outcomes is the side effect profile of psychotropic medications.\textsuperscript{14} A landmark study by Lazarou et al found that ADRs to be the fourth to sixth leading cause of death in the United States and serious ADRs accounted for 6.7\% of hospitalized admissions.\textsuperscript{15} Nearly 90,000 American adults are going to emergency rooms every year in response to adverse events (AEs) from psychiatric medications.\textsuperscript{16} The rate of adverse drug events (ADEs) during psychiatric hospitalization was reported to be 10.2 events per hundred admissions and ADRs are
the cause of 10 per 1000 patient-days in psychiatric hospitals.\textsuperscript{17,18} In Indian context, ADRs account for 35.4\% of emergency department visits,\textsuperscript{19} and they lead to 0.1-4.2\% of hospital admissions,\textsuperscript{20,21} and as many as 32.2\% of hospitalized patients experience ADR during their hospital stay.\textsuperscript{22} Polypharmacy, use of drugs with narrow therapeutic index and medical co-morbidities are the common factors which predispose the psychiatric patients to ADRs.\textsuperscript{23} In addition, drug interactions (DDIs) are the particular problem with psychiatric patients.\textsuperscript{24}

Individuals with psychiatric illnesses are at particular risk for DDIs because of the symptom-based prescribing, multiple prescribers, medical co morbidity and psychiatric co morbidity.\textsuperscript{25} Drug-drug interactions are major contributor to hospital admissions, treatment failures, avoidable medical complications, and subsequent health care costs.\textsuperscript{25,26} Drug interactions contribute to occurrence of ADRs both in the community and hospital settings.\textsuperscript{27,28} According to the published literatures the prevalence of potential DDIs (pDDIs) resulting in ADRs in different group of patients is estimated in the range of 1.3 to 60\%.\textsuperscript{28-32} It has been estimated that 26\% of ADRs requiring hospital admissions may be due to drug-drug interactions.\textsuperscript{33} The frequency of pDDIs in the psychiatric department is varied between 38.7 and 64.8.\textsuperscript{28,34-37} Psychotropic medications are the reason for 50\% of the ADRs in hospitalized psychiatric patients and many of which can be attributed to drug-drug interactions.\textsuperscript{32}

The burden of side effects contributes to noncompliance and reduction of quality of life (QoL).\textsuperscript{14} Often, this burden is not fully recognized and therefore reduces the overall effectiveness of a given agent. It is clear that ADRs are a source of additional economic burden on patients, care-givers and the healthcare systems that treat them.\textsuperscript{38} Drug related morbidity and mortality have been estimated to cause more than 136
billion dollars in an year in United States\textsuperscript{39} and in Indian studies it is ranging from Rs 412.76 – 1880 /ADR.\textsuperscript{40-43} Among the greatest challenges in treating the patients with mental illness, medication adherence, availability, cost and medication errors including adverse reactions have the greatest potential to compromise the therapeutic outcomes.\textsuperscript{14}

In the management of psychiatric patients, prevention or minimization of side effects should be an important part of the treatment plan, as the frequency and severity of side effects may play a role in the effectiveness and tolerability of the particular drug.\textsuperscript{44} Identification of these side effects requires careful consideration of other psychiatric and medical disorders that may mimic antipsychotic-related side effects. However, ADRs can perhaps be reduced by using less medication and with adequate knowledge of drug interactions and by collecting reliable information about their frequencies and possible risk factors.\textsuperscript{44,45} Monitoring of ADRs in psychiatry units can play a critical role in detecting ADRs and alerting physicians about the possibility and circumstances of such events, thereby protecting the patients from avoidable harm.
2. NEED FOR STUDY

Today’s drug development is focused on effective as well as safe and well tolerated medications. The safety and efficacy of antipsychotic, mood-stabilizers, antidepressant, anxiolytic and stimulant drugs have been established through a large number of randomized clinical trials. However, most clinical trials of psychotropics are conducted in “ideal” conditions, patients are selected according to stringent criteria and comorbid medical conditions are usually excluded. These trials are often short-term, lasting only for a few weeks or months. By contrast, the patients encounter in routine clinical practice is often having more complex presentations and comorbid medical illnesses, and they remain under care of a psychiatrist for longer periods of time. Also, patients do not respond to initial drug therapy may require several trials of different medications and combination of various drugs, which can increase the risk of adverse effects or drug interactions. In this context, ADRs that were not noticed in a trial become more apparent, and the burden of managing them falls on the practicing healthcare professionals.

Moreover, clinical development of most of the drugs happens in the developed countries, mainly in the west. Hence the efficacy and safety data available may not be applicable to Indian population due to the reasons like, difference in the prescribing practice, pharmaceutical preparation, and genetic variables. Studies on the adverse drug reaction of psychotropic medications are plentiful in number, but are carried out for short period of time (1-6 months). There is paucity of information on long term safety, especially on ADRs arising by drug-drug interaction. Also studies determining the predictors of ADRs to psychotropic agents and estimating the cost involved in the management of ADR are lacking. In the absence of much needed
information on risk-benefit ratio on psychotropic agents, the process of therapeutic decision-making to maximize the clinical effectiveness, minimize the ADRs and provide a cost benefit treatment is difficult. Therefore, this study aims to assess both short-term and long-term safety and tolerability of psychotropic agents in general and to determine the potential adverse drug interactions, preventability and predictors of ADRs and also the cost incurred in the management of ADRs in local psychiatric population.
3. OBJECTIVES OF THE STUDY

3.1 General Objective

- To study the profile of adverse drug reactions in hospitalized and ambulatory psychiatric patients.

3.2 Specific Objectives

- To determine the incidence and pattern of adverse drug reactions
- To assess predictability, preventability, severity and seriousness of ADRs
- To determine the predictors of short-term and long-term ADRs
- To determine the rate and pattern of potential adverse drug interactions
- To assess the cost impact of ADRs