4. LITERATURE REVIEW

4.1 Mental Health

Mental health is defined as a state of well-being where the individuals recognize their abilities and able to cope with the normal stresses of life, work productively and fruitfully, and make a contribution to their communities.\textsuperscript{2}

4.2 Mental Health Problems

A mental illness is a health problem that significantly affects the person feeling, thinking, behavior, and interaction with other people. Mental disorders, mental health problems, psychiatric disorders and psychiatric illness are the synonyms of mental health problem.\textsuperscript{68}

4.2.1 Types of mental health problems

Mental health symptoms are traditionally divided into ‘neurotic’ and ‘psychotic’ symptoms.\textsuperscript{1}

4.2.1.1 Neurotic Symptoms

Neurotic symptoms are also called as ‘common mental health problems’ and are the extreme forms of ‘normal’ emotional experiences such as depression and anxiety. This does not always mean that they are less severe psychotic symptoms.\textsuperscript{1}

4.2.1.2 Psychotic Symptoms

Psychotic symptoms are often associated with ‘severe’ mental health problems, which interfere with a person’s perception of reality and may include hallucinations, delusions or paranoia.\textsuperscript{1}
4.2.2 Magnitude of mental health problems

Mental health is the most common health condition, directly affecting about a quarter of the population in any one year. It is estimated that approximately 450 million people worldwide have a mental health problem and one in four families worldwide is likely to have at least one member with a behavioral or mental disorder.

4.2.3 Differences in the extent of mental health problems

Women (29%) are more likely to be affected by mental health problem than men (17%) but about 75% of people to die by suicide are men. It is reported that 20% of children have a mental health problem in any given year and about 10% at any one time. The rates of mental health problems among children increase as they reach adolescence. Older people are less likely to have a neurotic disorder and 25-40% of people with learning disabilities are estimated to have a mental health problem.

4.2.4 Burden of mental health problems

WHO’s Global Burden of Disease 2001 estimates that, 33% of the years lived with disability (YLD) are due to neuropsychiatric disorders. Four of the six leading causes of years lived with disability are depression, alcohol-use disorders, schizophrenia and bipolar disorder. Current predictions indicate that by 2030 depression will be the leading cause of disease burden globally. In addition to the health and social costs, those suffering from mental illnesses are also victims of human rights violations, stigma and discrimination, both inside and outside psychiatric institutions. The extent of the burden of mental disorders on family members is difficult to assess and quantify, and is consequently often ignored.
4.2.4.1 Economic Burden of Mental Health Problems

The economic impacts of mental illness include its effects on personal income, the ability of the persons with mental disorders or their caregivers to work and make productive contributions to the national economy, as well as the utilization of treatment and support services.\textsuperscript{80} The economic burden of mental illness in the US was estimated at $317.6 billion and in Europe (EU) at €240 billion, and in United Kingdom (UK) at £32 billion during last decade.\textsuperscript{81-84} Globally, the annual spending on mental health is less than US $2 and less than US $0.25 per person in high and low-income countries respectively. Median annual mental health expenditures per capita range from US $0.20 in low-income countries to US $44.84 in high-income countries. The aggregate cost of mental health problems thus increased by 36% for last few decades with a particularly large increase in the costs of health and social care.\textsuperscript{80-84}

4.3 Mental Health Problem in India

The study by the National Commission on Macroeconomics and Health (NCMH) shows that at least 6.5% of the Indian population has some form of serious mental disorders.\textsuperscript{85} Epidemiological studies done in the last two decades showed that the prevalence of mental disorders ranges from 18-207 per 1000 population with a median 65.4 per 1000 at any given time.\textsuperscript{86-92} Urban morbidity in India is 3.5% higher than the rural rate. The prevalence of schizophrenia and mood disorders has been considered as 3/1000 and 21/1000 respectively for all ages and both sexes.\textsuperscript{92-96} The rate for alcohol, cannabis and opiate use was reported to be 7-214/1000 population and 17% of alcohol users, 26% of cannabis users and 22% of opiate users were classified as dependent users based on International Classification of Diseases 10th
revision (ICD-10). Child and adolescent mental health problems are estimated to be 128/1000 (1–16 years) and mental retardation (MR) is reported to be 9.5/10,000 population of all ages. Geriatric mental health problems are assumed to be present among 31/1000 population above 60 years while the rates of dementia was reported to be 19/1000 in the 65+ years age group or 1.52/1000 population of all ages.

4.3.1 Causation in the Indian region

In India, deprivation and poverty are most strongly associated factors with mental disorders. Individuals with lower levels of education, low household income and lack of access to basic amenities are at high risk of mental disorder. Suicidal behavior was more common in females and are more predisposed to mental disorders due to rapid social change, gender discrimination, social exclusion, gender disadvantage like marrying at young age, concern about the husband’s substance misuse habits, and domestic violence. Divorced and widowed women are at slightly elevated risk of mental disorders in the country.

4.3.2 Economic burden of psychiatric disorders in India

India spends just 0.83% of its total health budget on mental health. Approximately 20 crores of the population require professional help. Each mentally ill patient requires Rs.500 per month for mental healthcare. This includes medication cost, doctor's fees and travelling cost to meet the doctor. Then the approximate total cost required per month will be Rs.10,000 crores. The burden of mental disorders is highest among young adults aged 15-44 years, which is the most economically productive section of the community. Unfortunately, mental illness requires medication for longer duration ranging from several months to years. Many of these
disorders if not detected early and treated, may become chronic and require medication for lifelong then the indirect costs in terms of loss of wages, disability, absenteeism and substance use is unimaginable. Above all, these families encounter social isolation, burden, stigma, poor quality of life and enormous psychological strain.101-104

4.3.3 Mental health disorders in the state of Karnataka

Around 25% of the state's population suffers from major mental health problems; shows a survey done by the newly formed Mental Health Task Force (MHTF).105 Out of the 25 percent who suffer from major mental or psychological disorders, 75% don't get treated and depression was the commonest diagnosis in the state.96, 91

4.3.4 Prevalence of mental health disorders in Mysore

A study conducted in Suttur (a village in Mysore district) found that 24.4% of the subjects were suffering from one or more diagnosable psychiatric disorder. Approximately 14.8% of them were diagnosed as depressive disorders as per ICD 10.91

4.4 Criteria for Diagnosis of Mental Health Problems

Mental disorders are classified by two major nosological systems, the International Classification of Diseases 10th revision106 and the Diagnostic and Statistical Manual of Mental Disorders fourth edition text revision (DSM IV-TR).107

4.4.1 International classification of diseases, 10th revision (ICD-10)

ICD 10 was published by the World Health Organization in 1992 and was designed to be used internationally for the classification of diseases. Chapter V of
ICD-10 deals with mental health disorders and it was divided into 10 major sections and 787 mental disorders.\textsuperscript{106}

4.4.2 Diagnostic and statistical manual of mental disorders (DSM- IV)

DSM- IV is published by the American Psychiatric Association in 1994 and covers only mental disorders. The DSM-IV-TR is in a five axis format and an updated version (DSM-V) was published in early 2013.\textsuperscript{107}

4.5 Treatment of Mental Health Disorders

Effective treatment of mental disorders involves a comprehensive package of care with the aim of addressing all of the person’s clinical, emotional and social needs, which includes combined psychosocial and pharmacological approach. The choice and combination of treatment is dependence on the type of mental illness, the severity of symptoms, the availability of options, decision determined by the individual in consultation with their health care providers.\textsuperscript{108}

4.5.1 Psychosocial therapy

Psychosocial therapy is often called as ‘talk therapy’ and are helpful in providing support, education and guidance to people living with mental illness and their families. Some common forms of psychosocial therapies are behaviors therapy, cognitive behavioral therapy (CBT), group therapy, psychoanalysis, psychoanalytic psychotherapy and family therapy.\textsuperscript{108-112} Symptom-focused psychotherapies such as cognitive-behavioral therapies have been shown to be efficacious for many of the psychiatric conditions. For mild and moderate depression, psychological treatments specifically cognitive behavior therapy computerized CBT (CCBT) and counseling can be as effective as drug treatments and should be offered as treatment
options.\textsuperscript{110-112} These days psychosocial treatments have been developed and tested by using modern methodologies.\textsuperscript{112}

### 4.5.2 Pharmacological therapy

Beginning in the early 1950s, effective psychotropic drugs were discovered for the pharmacological management of mental health disorders.\textsuperscript{108} Now a large number of medications are available, many of them have been shown to be effective in acute stages and in preventing relapses. The mechanism of action of these medications is mainly focused on the level of neurotransmission within the brain. Antipsychotics, antidepressants, mood stabilizers, anxiolytic and stimulant drugs are the commonly used class of drugs in psychiatric practices.\textsuperscript{108, 113}

### 4.5.3 Other therapy

In addition to medication and psychosocial treatment, other methods and interventions like electro convulsive therapy (ECT) repetitive transcranial magnetic stimulation (rTMS) are effective in managing and treating patients with mental illness.\textsuperscript{114, 115} Supplemental intervention like omega 3 fatty acids and folate also be an effective supportive management of mental illness in some patients.\textsuperscript{116-118}

### 4.6 Medication Adherence

Non-adherence is one of the most common causes of therapeutic failure in general and speciality clinical practices.\textsuperscript{119} One of the biggest challenges to the effectiveness of antipsychotic medications has been ensuring treatment adherence, and is defined as ‘the extent to which the patient follows medical instructions.’\textsuperscript{120, 121} The range of medication non-adherence reported to be 28% - 52% for major depressive disorder, 20%- 50% for bipolar disorder, 20%-72% for schizophrenia and 57% for anxiety
Approximately 40% of patients stop taking their prescribed antipsychotic medication within one year and about 75% of patients discontinue their medication within two years. Even with depot medication, about 25% of patients stop keeping scheduled appointments and no longer receive depot injections within an year after starting treatment. Suboptimal adherence to psychotropic medications has been associated with relapse, significantly more psychiatric hospitalizations, emergency room visits, poorer mental functioning, lower life satisfaction, more disability-related absences from work, greater substance use, increased suicidal behavior, poorer adherence to medications for co morbid medical conditions, and increased health care costs.

4.6.1 Reasons for medication non-adherence

Previous studies from the developed countries established reasons for non-adherence to antipsychotic medications, including limited insight, low therapeutic alliance, the presence of positive symptoms, co morbid substance abuse, unemployment, low social functioning and side effects. Although, there is a dearth of evidence on non-adherence from developing and under developing countries, studies from Africa reported that poverty, lack of family support, illness perspective and stigma, lack of insight, failure to treatment, long queues when attending for outpatient appointments were the important reasons for their non-adherence while in developing countries in Asian regions reported that financial problems, distance from hospitals, social and cultural myths, literacy and lack of insight and side effects are the reasons for their non-adherence.
4.7 Adverse Drug Reactions in Psychiatric Practices

Use of psychotropic drugs are associated with significant short-term and long-term safety concerns, including serious adverse drug reactions, affecting patients physical health and quality of life. Some adverse effects are predictable and depend on the size of the dose, while others are less predictable and may bear little relationship to the dose.

4.7.1 Prevalence of ADRs in psychiatric practices

Global prevalence of ADRs in the psychiatric department is varying from 3.6%-91%. The rate of ADRs during psychiatric hospitalization is reported to be 4.2-75% and ADRs were the cause of 10/1000 patients-days in a psychiatric hospital. A recently published database study reports that nearly 1 in 10 of all adverse drug event visits to emergency departments are due to psychotropic drugs and 9% of the patients from the psychiatric ward is transferred to the general wards due to ADRs. Adverse drug reactions were the reason for 7.5% of hospitalization in acute psychiatric ward and 25% of the admission were due to drug-induced psychiatric conditions. Approximately 12.3% of the death from ADRs in food and drug administration (FDA) MedWatch program is due to psychotropic medications. Among all the ADRs reported in children, 24% are psychiatric ADRs and one third of the ADRs reported in children were due to psychotropic medication. It is estimated that 35% of the geriatric population were suffering from ADRs due to psychotropic medication and attributable risk of falls due to commonly used psychotropic drugs was reported to be 1.7-2.0.
4.7.2 Nature of the problem

A review of range of articles related to the specific organ systems and psychotropic drugs identified that neurological adverse reactions, gastrointestinal system disorders and psychiatric disorders were the most frequent organ systems affected due to ADRs and accounted for approximately 40% of all ADRs.\textsuperscript{62, 142} Metabolic, cardiovascular, endocrine, reproductive, hematological, dermatological and respiratory categories (in descending order of frequency) accounting for the balance.\textsuperscript{63-67,143,144}

4.7.2.1 Cardiovascular Effects

Psychotropic drugs can produce cardiovascular side effects associated with a degree of cardiotoxicity.\textsuperscript{148,149} The coexistence of a heart disease complicates the management of mental illness, can contribute to a reduced quality of life and a worse illness. Some types of antidepressants and antipsychotic drugs have various cardiovascular side effects that can lead to cardiovascular complications, especially cardiac arrhythmias, which in some cases have resulted in death of people with no previous cardiac history.\textsuperscript{150}

4.7.2.1. a Orthostatic hypotension

Orthostatic hypotension is the most common adverse autonomic side effect of antipsychotic drugs. The orthostasis occurred by $\alpha_1$ adrenergic blockage and within few days of therapy or when increasing the dose, tolerance will occurs within 2-3 weeks.\textsuperscript{151} Different classes of antipsychotic drugs have differing propensities to cause autonomic nervous system dysfunction. Low potency drugs (chlorpromazine and thioridazine) are more likely to cause significant hypotension than mid- to high-potency drugs. Atypical antipsychotics are also associated with bradycardia and
hypotension.\textsuperscript{152} For example, 19\% of 342 clozapine-treated patients reported dizziness, but a drop in systolic blood pressure following a change in posture was detected in only 9\%.\textsuperscript{152} Similarly, dose-effectiveness trials of quetiapine in 2300 patients reported a prevalence of dizziness in 10\% but hypotension in only 7\%.\textsuperscript{153}

\textbf{4.7.2.1.b QTC prolongation}

The use of TCA and neuroleptics have long been associated with prolongation of the QTc, development of torsade de pointes that can cause syncope and may progress to ventricular fibrillation and sudden death.\textsuperscript{154-155} Amitriptyline, doxepin, desipramine, imipramine, and clomipramine have been associated with a prolonged QT interval, whereas thioridazine was the most potent neuroleptic causes QT prolongation and arrhythmia.\textsuperscript{156,157} Discontinuation of suspected drug has been recommended for if the interval consistency exceeded 500 msec.

\textbf{4.7.2.2 Endocrine and Metabolic Side Effects}

Antipsychotic related metabolic and endocrine abnormalities are most worrisome, as they are risk factor for cardiovascular disease, insulin resistance and diabetes mellitus, leading to increased morbidity and mortality but may also impaired the patient adherence to treatment. Importantly, children and adolescents may be more sensitive to antipsychotic agents related adverse events than adults.\textsuperscript{158} These metabolic effects may pose a burden as serious as the extrapyramidal side effects.\textsuperscript{159} Tricyclic antidepressants, mono amine oxidase inhibitors, lithium and antipsychotics have also shown major metabolic side effects related to weight gain.
4.7.2.2.a Weight gain

Long-term administration of psychotropic induces excessive weight gain, which affects up to 50% of patients. Weight gain tends to occur within the first months of treatment and the pattern of weight gain has been found to vary with different agents. Among the atypical antipsychotics weight gain is most common with clozapine and olanzapine. It is a major side effect of the main mood stabilizers. Chronic treatment with lithium is associated with increased weight, reaching more than 10 kg in 20% of patients. Among the antidepressants, tricyclic antidepressants and monoamine oxidase inhibitors are more likely to cause weight gain than the SSRIs or the newer antidepressant except mirtazapine.

4.7.2.2.b Hyperprolactinemia

Hyperprolactinemia is a clinically important adverse event of psychotropic medication commonly, conventional antipsychotics are associated with hyperprolactinaemia but there have also been reports of antidepressants causing hyperprolactinaemia. Antidepressant drugs with serotonergic activity, including selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and some tricyclics, can cause hyperprolactinemia. Among the atypical agents and or a lesser extent olanzapine produces a dose related increase in prolactin level during the first week of therapy which exceeded than that seen in haloperidol. A prospective study of children and adolescents found elevated prolactin levels observed in 71% of those treated with risperidone compared with lower rates in those treated with olanzapine or quetiapine. A long-term (206 days) randomized trial of 555 patients with first episode psychosis found a greater elevation of prolactin levels in those treated with risperidone (mean modal dose 3.3 mg) than in those treated with haloperidol (modal dose 2.9 mg).
4.7.2.2.c Diabetes mellitus

The prevalence of Type 2 diabetes mellitus (Type 2 DM) and the metabolic syndrome is significantly higher in patients with chronic psychiatric disease, particularly schizophrenia and major mood disorders. A retrospective cohort study showed that the prevalence of diabetes was over 20%, with no significant difference between second generation antipsychotics or first-generation antipsychotics (FGAs). It has been reported that 6.9% of patients receiving SGAs developed new-onset type-2 DM over one-year period, and the risk was higher with olanzapine, clozapine exposure, while quetiapine and risperidone showed no effect relative to haloperidol. According to a large observational study long-term use of antidepressants in at least moderate daily doses was associated with an increased risk of diabetes. This association was observed for both tricyclic antidepressants and selective serotonin reuptake inhibitors.

4.7.2.2.d Disturbances of lipid metabolism

Data about therapy of psychotropic drug-induced dyslipidaemia are scarce and literature on concomitant lipid lowering medication is limited to case reports. It was found that clozapine and olanzapine, were associated with increase in cholesterol and triglyceride levels at the end of an 8-week treatment. Another comparative study, reported a significantly high triglyceride levels in 56% of clozapine, 39% of olanzapine and 21% of risperidone-treated patients compared to none of haloperidol and 8% of fluphenazine-treated patients. The same study showed a reduction of high density lipoprotein (HDL) cholesterol during treatment with clozapine and olanzapine, whereas total cholesterol levels were significantly lower in risperidone and fluphenazine treated patients.
4.7.2.3 Dermatological Side Effects

Dermatological side effects are uncommon with psychotropic medicines. The majority of adverse cutaneous events are benign and easily treated, and do not place the patient at a serious health risk.\(^{176}\) The most frequently reported cutaneous adverse effects include: exanthematous eruptions, skin pigmentation changes, photosensitivity, urticarial, pruritus and alopecia.\(^{177}\) All antipsychotic, antidepressant and mood stabilizing drugs are reported with some or other forms of cutaneous adverse reactions.\(^ {178}\)

4.7.2.4 Hepatic Dysfunction

Hepatotoxicity of psychotropic drugs occurs in a variable but small proportion of users and therefore can be considered unpredictable or idiosyncratic.\(^ {179}\) Benign elevation in liver function test (LFTs) has long been reported early in the course of therapy with most of the antipsychotics and antidepressants.\(^ {180}\) In addition, antipsychotics have been associated with both hepatic and cholestatic liver injury. Elevations of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) more than 2-3 times of normal values have been reported in up to 50% of patients on clozapine, 14% of patients on risperidone, and 24% of those on olanzapine.\(^ {181}\) Most tricyclic antidepressants are potentially hepatotoxic while it was very rarely reported with serotonin reuptake inhibitors such as fluoxetine and paroxetine.\(^ {182, 183}\)

4.7.2.5 Hematological Side Effects

Almost all classes of psychotropic agents have been reported to cause blood dyscrasias including neutropenia. Mechanisms include direct toxic effects upon the
bone marrow, the formation of antibodies against haematopoietic precursors or involve peripheral destruction of cells. Agranulocytosis is probably the most important drug-related blood dyscrasia.\textsuperscript{184,185} Of drugs encountered in psychiatry, antipsychotics including clozapine (risk of agranulocytosis approximately 0.8%, predominantly in the first year of treatment) and phenothiazines (chlorpromazine agranulocytosis risk approximately 0.13%), and antiepileptics (notably carbamazepine, neutropenia risk approximately 0.5%) are the most common causes of drug-related neutropenia/agranulocytosis.\textsuperscript{184,185}

4.7.2.6 Neurologic Side Effects

The neurological side effects of psychotropics include movement disorders such as tardive dyskinesia and acute EPS, Neuroleptic Malignant Syndrome (NMS), seizures, sedation and other cognitive effects. They can add a significant burden, reducing patients’ quality of life and contributing to noncompliance.

4.7.2.6.a Sedation

Sedation is a property of many psychotropic drugs. Many of the neuroleptic, anxiolytic, antidepressant and antihistamine drugs were extremely sedative. Sedation is now increasingly considered as an adverse effect which should be avoided rather than a desirable effect especially when treating disorders such as anxiety or depression.\textsuperscript{186,187}

4.7.2.6.b Extra pyramidal side effects

EPS is a broad term that describes several types of acute and chronic movement disorders. Acute dystonias, parkinsonism and akethesia occurs early in the treatment. Whereas TD have late onset, usually occurs after years of treatment.\textsuperscript{188} It has been
reported that 60% of the patients who receive typical antipsychotic agents develop some forms of EPS. Meta-analyses indicate that, when SGAs are used at recommended doses, they are associated with significantly lower rates of extrapyramidal side effects compared with (generally high-potency) conventional antipsychotics.\textsuperscript{188,189} On the basis of available data, tardive dyskinesia appears to occur significantly less frequently with clozapine, risperidone, olanzapine and quetiapine than with typical antipsychotics.\textsuperscript{189} EPS have been also reported with different classes of antidepressants, are not dose related, and can develop with short-term or long-term use. Duloxetine, sertraline, escitalopram, bupropion and amitryptyline are commonly implicated for development of EPS.\textsuperscript{190}

4.7.2.6c Anticholinergic side effects

Psychotropic drugs are often liable to unwanted anticholinergic effects that reduce tolerance and compliance. Less dangerous but troublesome anticholinergic effects includes dry mouth, constipation, tachycardia, blurred vision and urinary retention occurs in 50% of the patients treated psychotropic medication.\textsuperscript{191} Tricyclic antidepressants produce a greater incidence of anticholinergic effects than SSRIs. Anticholinergic effects usually benign but may sometimes be clinically significant.\textsuperscript{192,193}

4.7.2.7 Ophthalmic Side Effects

All psychotropic medications have the potential to induce numerous and diverse unwanted ocular effects. The disorders of the eyelid and of the keratoconjunctiva are mainly related to phenothiazines and lithium. Chlorpromazine commonly cause abnormal pigmentation of the eyelids, interpalpebral conjunctiva and cornea. Uveal tract problems are mainly associated with tricyclic antidepressants, typical
antipsychotics, topiramate and selective serotonin reuptake inhibitors. TCAs, typical antipsychotics and SSRIs can all cause mydriasis. Other visual problems of special concern are the ocular dystonias, other eye movement disorders, and decreased ability to perceive colours and to discriminate contrast. Ocular dystonias can occur with antipsychotics (especially high-potency ones), carbamazepine (especially in polytherapy), topiramate and, rarely, with SSRIs. Disturbance in various eye movements is frequently seen with benzodiazepines, antiepileptic drugs and lithium. Impairment in the perception of colours and the discrimination of contrasts has been shown to occur not uncommonly with carbamazepine and lorazepam.  

4.7.2.8 Sexual and Reproductive Side Effects

The prevalence of sexual dysfunction associated with neuroleptics was 60% in men and 30–93% in women. It include anorgasmia, unsatisfying or painful orgasm, altered libido, erectile failure, priapism, menstrual irregularities, delayed or retrograde ejaculation and altered sexual sensation and sensitivity. Benzodiazepines, lithium, monoamine oxidase inhibitors, neuroleptics, and tricyclic antidepressants are more likely to cause sexual dysfunctions.

4.7.3 Extent of the adverse drug reaction

Severity of the ADRs in psychiatric patients varying from mild sedation to suicidality and death. A total of 33 instant of suicidality were reported in AMSP (Arzneimittelsicherheit in der Psychiatrie) study between 1993 to 2008 in 54 psychiatric hospitals. In the ambulatory psychiatric patients, 43% of the ADRs were preventable. Avoidability of ADRs in hospitalized patients was ranges from 13% to 29.7%. In a recently published article, preventable ADRs (pADRs) resulted in change in therapy, and 21% resulted in transfer to a medical facility.
4.7.4 Range of agents implicated

Drugs classes most commonly associated with adverse reactions in psychiatric patients were antipsychotics and antidepressants that account for approximately 90% of all ADRs. The antipsychotic agents in question were second-generation antipsychotics or conventional antipsychotics. Second-generation antipsychotics were associated with metabolic ADRs whereas conventional antipsychotics with neurological ADRs. Among the antidepressants selective serotonin receptor inhibitors and tricyclic antidepressants were the most commonly implicated class of drug with ADRs.

4.7.5 Short-term ADRs

During the early phases of treatment with psychotropic medications, patients may experience ADRs such as sedation, orthostasis, restlessness, muscle spasms, tremor, dry mouth, constipation and blurring of vision. These reactions are predominantly dose related and can be attributable to drug’s actions to serotoninergic, histaminic, cholinergic, dopaminergic and noradrenergic receptors. A large amount of the short-term ADRs are self-limiting and can be corrected by dose reduction.

4.7.6 Long-term ADRs

Mental health disorders are chronic and recurrent, so long-term side effects are really more important than acute ones in terms of patient compliance and quality of life. ADR that occurs after 180 days of initiation of the suspected drug is considered as long-term ADRs. Sexual dysfunctions, diabetes mellitus, weight gain and tardive dyskinesia were the commonly reported long-term ADRs.
4.7.7 Reasons for occurrence of ADRs

The main reasons for occurrence of ADR associated with the use of psychotropic medications could be due to their effects on neurotransmitters.\textsuperscript{204} Also, there is a reciprocal relationship between dopamine and acetyl choline (ACH) in the sympathetic and parasympathetic nervous system that cause a very uncomfortable potentially widespread side effects. Additionally, there is an inverse relationship in the sympathetic nervous system between dopamine and serotonin. If dopamine is blocked, serotonin level increases resulting in both therapeutic effects and side effects.\textsuperscript{204}

4.7.8 Drug induced psychiatric conditions

Drug induced mental health disorders are relatively common. A recently published study identified that 25\% of the ADRs related admitting diagnosis was drug-induced psychiatric conditions. Another study conducted in children reported that 24\% of all the ADRs were psychiatric ADRs.\textsuperscript{55,143} The risk of an individual to experience psychiatric reactions is greater if mental illness is present or has occurred in the past. Other predisposing factors include impaired cerebral function (elderly or patients with brain damage), alcohol or drug abuse, concurrent physical diseases and stressful environment.\textsuperscript{205} Other than steroids, antiretroviral therapy, antiepileptic, antiparkisonian agents, antineoplastic and drugs that target the endocrine system are commonly reported with psychiatric side effects like irritability, psychosis, mood disorders, hallucinations and sleep disturbances.\textsuperscript{206}
4.7.9 Management of ADRs

Management begins with awareness of potential for ADRs, not only for psychiatric drugs but also for the co-prescribed non-psychiatric drugs.23 Number of psychiatric drugs like lithium and clozapine require pre-commencement blood screening. In addition, there is a need for routine and ongoing monitoring while prescribing either drugs.23 Rapid action is sometimes important because of the serious nature of the reaction (dystonia). If the patient’s medical condition cannot managed without a medicine that has caused adverse reaction, patient need to treat symptomatically while continuing the suspected drug. If the culprit drug is fairly clear, based on the benefit-risk ratio the drug can be withdrawn or an equally beneficial substitute unlikely to produce the same ADR can be started. However, when treating an ADR, it is important not to introduce more medicines than are essential.207

4.7.10 Economic impact of ADRs

Adverse drug reactions have been reported with significant impact on health care cost. In an Australian study, 5.7% of all admissions were drug related, out of which 4.9% were due to ADRs, resulted in a calculated cost of > €2 million, or €3077 per patient.208 In a study conducted in Germany estimated that direct cost associated with ADRs was 0.4 billion dollars annually.209 In studies reported from US210 revealed that the cost involved in the management of ADRs per patient was in the range of US $2000 to US $4000. Wasserfallen et al211 reported that a mean length of stay of nine days in a hospital attributes to ADRs resulting in a cost of €3122 per ADR. Moore et al212 reported that the average cost involved in the ADRs was €2900, and Lagnaoui et al213 reported that the mean cost associated with the management of ADRs was €2700 per patient in a department of internal medicine. In India, Ramesh et al42
reported that the cost associated in treating all reported ADRs was US $1595, with average US $15 per ADR. Thiyagu et al 214 study from India showed that the total cost incurred due to ADRs resulting in hospitalization found to be US $36451 with average US $115 per hospitalized patients.

4.8 Adverse Drug Interaction

Potential drug-drug interactions are very frequent in psychiatric practices and result in poor tolerability or reduced efficacy, or both, which can negatively impact patient outcomes.34 Old age, taking increased number of medications, long hospital stay, gender and comorbid conditions have been reported as common risk factors for DDIs.29-33 Clinically significant drug-drug interactions are the ones which can result in changes of therapeutic effect of one of the two drugs or results in adverse drug reactions and may leads to an increased risk of hospitalization and higher health care cost. In comparison to other clinical speciality wards, e.g., internal medicine wards very few studies have addressed the issue of adverse drug interaction (ADIs) in psychiatric wards.29,30 According to a study conducted in France, around 40% of ADRs reported with SSRIs were related to DDIs.215 Drug-drug interactions are usually classified as pharmacokinetic, pharmacodynamic and pharmaceutical interactions.

4.8.1 Pharmacokinetic drug-drug interactions

Pharmacokinetic drug-drug interactions occur when one drug (perpetrator) changes the systemic concentration of another drug (the object), altering ‘how much’ and for ‘how long’ the object drug is present at the site of action. Pharmacokinetic interactions affect absorption, distribution, metabolism and elimination of the object drug.115, 27,216
4.8.1.1 Drug Absorption Interactions

Drug interactions can occur when one drug changes the absorption characteristics of another drug. The binding of one drug to another, changes in gastric pH and changes in gastrointestinal motility can cause these drug interactions.\textsuperscript{24} Important clinical effects caused by changes in drug absorption are rarely seen in general medical or psychiatric practice. An example of an undesirable interaction is the decreased absorption of phenothiazines or sulpiride when they are taken concurrently with antacids, leading to a reduced antipsychotic effect.\textsuperscript{24}

4.8.1.2 Drug Distribution Interactions

Alteration in protein binding is the most common drug-drug interaction affecting drug distribution. This type of interaction occurs when there is a competitive inhibition for protein binding sites.\textsuperscript{217} The most clinically significant interactions involve with drugs that are highly protein bound; have a narrow therapeutic index; and drugs having small volume of distribution.\textsuperscript{24} A classic example of this type of drug-drug interaction is the interaction between diazepam and phenytoin. Diazepam replaces the phenytoin from plasma proteins, resulting an increased plasma concentration of free phenytoin and an increased risk of adverse effects.

4.8.1.3 Lysosomal Trapping

Recently another mechanism of interaction involving drug distribution at a cellular level has been described. Basic lipophilic compounds like TCAs and SSRIs are taken up by acidic compartments in the cell. This involves either association with phospholipids in the cell membrane or lysosomal trapping within the cell. Lungs, liver and kidneys are rich in lysosomes and take up most of the trapping susceptible drug in
the body. Drugs that are trapped by lysosomes compete each other for uptake into the organelles. Mutual inhibition of lysosomal trapping results in higher plasma drug concentrations. This will have the greatest effect on tissues with a low density of lysosomes, such as the heart. This interaction may contribute to the increased cardiotoxicity of drugs such as thioridazine when co-prescribed with antidepressants.\textsuperscript{218,24}

\subsection*{4.8.1.4 Drug Metabolism Interactions}

The most clinically important type of pharmacokinetic drug-drug interactions are those altering a drug’s metabolism.\textsuperscript{27} There are several enzyme families involved in drug metabolism and the cytochrome P450 is the most important. Some drugs may be metabolized by more than one isoenzyme. Therefore, when one enzyme system is inhibited or induced by an interacting drug, a clinically significant interaction may or may not occur. For example, tricyclic antidepressants are metabolized by CYP2D6, CYP1A2 and CYP3A4. Inhibition or genetic absence of one isoenzyme can lead to compensation through the secondary isoenzyme pathway.\textsuperscript{219}

\subsection*{4.8.1.5 Drug Elimination Interactions}

Many drugs and drug metabolites are excreted in the urine via renal tubular secretion. Drugs that use the same active transport system in the tubule can compete with each other and result in decreased elimination and potentially toxic serum concentration.\textsuperscript{219} The most important of these in psychiatric practice are interactions with lithium. Lithium is filtered by the kidney and reabsorbed by the proximal renal tubule in parallel with sodium. A sustained increase in urinary sodium excretion such as that produced by thiazide diuretics promotes a compensatory reabsorption of sodium by the proximal renal tubule. Lithium reabsorption is similarly enhanced, and because it
has a narrow therapeutic index this can increase the plasma lithium concentration to potentially toxic levels.\textsuperscript{26, 27}

4.8.2 Pharmacodynamic drug-drug interactions

The most common interactions encountered in clinical practice are pharmacodynamic interactions. They occur when drugs compete for the same receptor or produce antagonistic or synergistic effects on the same target organ or system.\textsuperscript{24, 27}

4.8.2.1 Additive or Synergistic Interactions

Often, drugs are used in combination to take advantage of their similar pharmacodynamic effects. However, it is the unintentional additive or synergistic effects of medication that leads to adverse drug interactions.\textsuperscript{219} In many cases, it is the secondary pharmacological actions of the drugs, which are quiet often overlooked, that are responsible for clinically significant drug interactions. The atypical antipsychotics are a good example for secondary pharmacologic activities. Although the main pharmacological activity of antipsychotics is through their effect on dopamine receptors, they may unintentionally augment the effects of antihypertensive medications by blocking $\alpha_1$-adrenergic receptors and cause untoward orthostatic hypotension that could be responsible for falls in elderly patients.\textsuperscript{219}

4.8.2.2 Antagonistic or Opposing Effects

Many instances of antagonism are beneficial: for example, in augmentation treatment of resistant depression with lithium and an anti-depressant. By contrast, SSRIs increase the risk of gastrointestinal bleeding when taken with aspirin or other non-steroidal anti-inflammatory drugs, because of a synergistic inhibition of platelet aggregation.\textsuperscript{24, 27} In contrast to additive drug interaction, combining drugs with
opposing effects can result in loss of drug efficacy. For example, antipsychotic drugs reduce the efficacy of levodopa in parkinson’s disease by blockade of dopamine receptors in the corpus striatum.\textsuperscript{24}

\textbf{4.8.3 Pharmaceutical interactions}

Pharmaceutical interactions occur prior to administration when drugs are mixed outside the body. For example, the incompatibility of phenobarbital with chlorpromazine or opioid analgesics when mixed in the same syringe. When compared to the other two interaction mechanisms pharmaceutical interactions are least likely to cause problems in clinical practice in particular with psychotropic drugs.\textsuperscript{24}

\textbf{4.9 Role of Clinical Pharmacist in Psychiatric Practice}

Efforts to improve the outcomes of patients with mental illness often have involved incorporating the skills of a variety of health care professionals into collaborative care models.\textsuperscript{220} For last 30 years, clinical pharmacists have contributed to these care models in capacities ranging from educator to consultant to provider.\textsuperscript{220} They incorporate interventions into the care of their patients with the use of different strategies such as patient education, drug monitoring and management of adverse reactions.\textsuperscript{221-223} Studies have shown that introduction of clinical pharmacy services to the psychiatric department was associated with a significant reduction in the number of medications (both total and psychotropics), increase in the medication adherence and reduction of cost per prescription and total care cost.\textsuperscript{222-225}