CHAPTER 2

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2.0 REVIEW OF LITERATURE

2.1. Psychiatric disorders

Psychiatric disorders, also known as mental illnesses, are extraordinarily common and have a profound impact on well-being and functional status. Collectively, psychiatric disorders account for more aggregate disability than do those involving any other organ system (Goldman Lee & Schafer Andrew, 2012). Psychiatric disorders are central nervous system diseases characterized by disturbances in emotion, cognition, motivation, and socialization. As a result of their high prevalence, early onset, and persistence, they contribute substantially to the burden of illness worldwide. Most psychiatric disorders are heterogeneous syndromes that currently lack well-defined neuropathology and bonafide biological markers. Global burden of disease statistics indicate that 4 of the 10 most important causes of disease worldwide are psychiatric in origin (Longo DL and others, 2012)

Mental disorders are not only highly prevalent medical conditions but they are also highly disabling. Measured by years lived with disability (YLD) and by premature death in disability adjusted life years (DALYs), psychiatric and neurological conditions accounted for over 13% of the global disease burden in the year 2001. When compared with 1990, the contribution of neuropsychiatric disorders is expected to increase to almost 15% by the year 2020. (Kohn R et al. 2004)

The prevalence of disease is the estimated number of cases per 1,000 persons at risk in a population at a given time (point prevalence) or over a defined period (period prevalence) (Sadock, Sadock & Ruiz, 2009). The worldwide prevalence of schizophrenia estimates range between 0.5% and 1%.

Age of first episode is typically younger among men (about 21 years of age) than women (27 years). Of persons with schizophrenia, by age 30, 9 out of 10 men, but only 2 out of 10 women, are likely to manifest the illness. Persons with schizophrenia pose a high risk for suicide. Approximately one-third are likely to attempt suicide and, eventually, about 1 out of 10 are likely to take their own lives. The economic burden of schizophrenia is particularly great during the first year following the index episode, relative to the third year onwards. This finding suggests the need for improved monitoring of persons with schizophrenia upon initial diagnosis. (CDC, 2011).

An incidence rate (the estimated annual number of first-onset cases in a defined population per 1,000 persons at risk) A systematic review of incidence data from some 160 studies from 33 countries, published between 1965 and 2001, yielded a median value of 0.15 and mean value of 0.24 per 1,000, with a fivefold range of the rates and a tendency for recent studies to report lower rates (Sadock, Sadock & Ruiz, 2009). Even for the most severe mental disorder, schizophrenia, at least one-third of individuals remain untreated. Estimates of the median treatment gap (%) by South-East Asia WHO region is estimated to be 28.7%. Clearly, the rates presented are an underestimation (Kohn R et al., 2004).
2.2. Psychosis

Schizophrenia is the prototypical psychotic disorder. (Goldman Lee & Schafer Andrew (Eds.) 2012) Psychosis (spelled as sy-KOH-sis comes from the Greek ψυχή "psyche", for mind/soul, and -ωσις "-osis", for abnormal condition) means abnormal condition of the mind, and is a generic psychiatric term for a mental state (Fig. 1. Kablinger A.S., 2011). Psychosis is a syndrome, which is a mixture of symptoms that can be associated with many different psychiatric disorders but is not a specific disorder itself in diagnostic schemes such as DSM-IV or ICD-10 (Stahl SM, 2008).

Psychosis is a mental state a mental state often described as involving a "loss of contact with reality". People experiencing psychosis may report hallucinations or delusional beliefs, and may exhibit personality changes and disorganized thinking (Kablinger A.S., 2011), often behaving very differently from the way they usually do. It affects the way a person thinks, feels and behaves (Julie O’Sullivan & Jillian Gilbert, July 2010). Therefore, psychosis can be considered to be a set of symptoms in which a person’s mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others are impaired. Psychotic disorders have psychotic symptoms as their defining features, but there are other disorders in which psychotic symptoms may be present but are not necessary for the diagnosis (Stahl SM, 2008).

A psychotic episode occurs in three phases. The length of each phase varies from person to person. Phase 1: Prodrome: The early signs may be vague and hardly noticeable. There may be changes in the way some people describe their feelings, thoughts and perceptions, which may become more difficult over time. Phase 2: Acute: Clear psychotic symptoms are experienced, such as hallucinations, delusions or confused thinking. Phase 3: Recovery: Psychosis is treatable. The pattern of recovery varies from person to person. (Julie O’Sullivan & Jillian Gilbert, 2010)

2.2.1. The Disorders in Which Psychosis is a Defining Feature

In addition to the primary psychoses a number of psychiatric and somatic conditions can produce psychotic symptoms. Following are different types of psychoses (Julie O’Sullivan & Jillian Gilbert, July 2010).
a) First episode psychosis
This refers to the first time someone experiences psychotic symptoms or a psychotic episode. People experiencing a first episode may not understand what is happening. The symptoms can be highly disturbing and unfamiliar, leaving the person confused and distressed. With the right help, a large percentage of individuals may never experience another psychotic episode. A proportion may develop a more long-term illness and require ongoing treatment.

b) Drug Induced Psychosis
These are symptoms of psychosis that result from the use of or withdrawal from alcohol or other substances (e.g., illicit drugs). For most people, the symptoms of psychosis will abate as the effects of the substance wear off. However, a significant proportion may develop a more long-term psychotic illness.

c) Organic Psychosis
The presence of psychotic symptoms due to a physical illness or problem (e.g., head injury, brain tumor, encephalitis, AIDS).

d) Brief Reactive Psychosis
Symptoms of psychosis are triggered by a traumatic event or extremely stressful life events (e.g., death of loved one, traumatic accident). While symptoms are severe, the person usually recovers in a short time span.

e) Schizophrenia
(A) Two (or more) of the following characteristic symptoms, each present for a significant portion of time during a 1-month period (or less if successfully treated) (1) delusions (2) hallucinations (3) disorganized speech (e.g., frequent derailment or incoherence) (4) grossly disorganized or catatonic behavior (5) negative symptoms (e.g., affective flattening, alogia, or avolition). (B) Social/occupational dysfunction. For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet the first (A) criterion (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms (DSM IV criteria). Other symptoms experienced may include diminished motivation, social withdrawal, reduced interaction and communication, impaired concentration, and diminished insight into being unwell.

f) Schizophreniform Disorder
Where a diagnosis of schizophrenia is likely, but the symptoms have been present for less than six months.
g) Bipolar Affective Disorder

A condition where the person experiences feelings of mania (highs) and feelings of depression (lows). The psychosis tends to relate to the person's mood state at that time, for example, hearing derogatory voices when depressed or believing they have magical powers when manic.

h) Schizoaffective Disorder

A condition where the person experiences both a mood disorder (manic and depressive symptoms) and a psychotic illness concurrently.

i) Psychotic Depression

A severe depressive illness with psychotic symptoms

Schizophrenia is a clinical syndrome characterized by a mixture of clinical features referred to as psychosis and entails profoundly disruptive, psychopathology that involves disturbances in cognition, emotion, perception, thinking, and behavior (Sadock BJ and Sadock VA, 2010). It is a heterogeneous disorder with functional deterioration in the major arenas of life, such as interpersonal relations, education, employment, and self-care (Jibson et al, 2004). Schizophrenia is arguably the most puzzling of psychiatric syndromes and one of its most debilitating. The expression of these manifestations varies across patients and over time, but the effect of the illness is always severe and is usually long-lasting. (Sadock, Sadock & Ruiz, 2009)

Schizophrenia most often starts in late adolescence. The disorder usually begins before age 25, persists throughout life, and affects persons of all social classes. Both patients and their families often suffer from poor care and social ostracism because of widespread ignorance about the disorder. Although schizophrenia is discussed as if it is a single disease, it probably comprises a group of disorders with heterogeneous etiologies, and it includes patients whose clinical presentations, treatment response, and courses of illness vary. (Sadock, Sadock & Ruiz, 2009)

Generally, symptoms of schizophrenia are categorized by Positive symptoms (an excess or distortion of normal functions) such as hallucinations (false perceptions), delusions (false beliefs); Negative or Deficit symptoms (diminution or loss of normal functions) such as flattened affect (restricted range of emotions), poverty of speech, anhedonia (diminished capacity to experience pleasure), and asociality; Disorganized thoughts or bizarre behavior and Cognitive deficits (impairment in attention, processing speed, working memory, abstract thinking, problem solving, and understanding of social interactions) and Occupational and Social dysfunction. (Bustillo JR, 2008)

Schizophrenia is well established as a brain disorder, with structural and functional abnormalities visible in neuroimaging studies and a genetic component, as seen in twin studies. The disorder is usually chronic, with
a course encompassing a prodromal phase, an active phase, and a residual phase. The active phase has symptoms such as hallucinations, delusions, and disorganized thinking. The prodromal and residual phases are characterized by attenuated forms of active symptoms, such as odd beliefs and magical thinking, as well as deficits in self-care and interpersonal relatedness. Although schizophrenia is discussed as if it is a single disease, it probably comprises a group of disorders of heterogeneous etiology (Sadock BJ and Sadock VA, 2010).

2.3. Schizophrenia - History

The history of schizophrenia is the history of psychiatry. The word “schizophrenia” is less than 100 years old (Mathias K, 2011) but it has probably accompanied mankind throughout its whole history (Kyziridis TC, 2005). The illness itself is generally believed to have accompanied mankind through its history. Written documents that identify Schizophrenia can be traced to the old Pharaonic Egypt, as far back as the second millennium before Christ (History of schizophrenia. Schizophrenia.com, 2010). Early Greek physicians described delusions of grandeur, paranoia, and deterioration in cognitive functions and personality (Sadock BJ and Sadock VA, 2007). Hindu descriptions date back to approximately 1400 BC and can be found in the Atharva Veda, one of the 4 Vedas, which are primary texts of Hinduism. The Vedas contain hymns and incantations from ancient India. It has been posited that health resulted from a balance between 5 elements (Bhuthas) and 3 humours (Doshas) and that an imbalance between these various elements might result in madness (Kyziridis TC., 2005). The descriptions of various mental illnesses in ancient Indian texts are probably the oldest such accounts. Two well-known Ayurvedic manuscripts, the Charaka Samhita by Charaka, and the Sushruta Samhita by Sushruta, have established the roots of modern Indian medicine. The tridoshic philosophy is still widely accepted among modern Indian patients. The history of psychiatry in India has witnessed major changes in the past. The great saga 'Agastya' formulated a treatise on mental diseases called as 'Agastiyar Kirigai NooT', in which 18 psychiatric disorders with appropriate treatment methods were described. (Nizamie and Goyal, 2010). In the ancient texts of Ayurveda, there are detailed descriptions of mental disorders known as “Unmada”, and schizophrenia can be correlated with many of the types of “Unmada”. Ayurvedic physicians describe schizophrenia as a disorder of the mind caused by the doshas (vata, kapha, and pitta) moving in the wrong paths due to increased toxicity. According to the classical Ayurvedic texts, the Charaka Samhita, insanity is defined as, “the perversion of the mind, intellect, consciousness, knowledge, memory, desire, manners, behavior, and conduct”. It is denominated as insanity (unmada) because it is madness(mada) of the mind caused by a deviation (unmarga) of the humors” (Swami Sada Shiva Tirtha, 1998). The ancient Indian scripture, Atharva-Veda, mentions that mental illness may result from divine curses. Descriptions of conditions similar to schizophrenia and bipolar disorder appear in the Vedic texts. A vivid description of schizophrenia is also found in Atharva-Veda. Great epics such as the Ramayana.
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and the Mahabharata made several references to disordered states of mind and means of coping with them. The Bhagavad Gita is a classical example of crisis intervention psychotherapy. Another interesting contribution of the Ayurveda is its knowledge regarding the diet-disease relationship and the association of a disease with a specific physical constitution. Diagnosis was entertained by the five senses and supplemented by interrogation. Close to the roots of Hindu mythology, Najabuddin Unhammad (1222 AD), an Indian physician propagated the Unani system of medicine as he described seven types of mental disorders, Sauda- a-Tabee (schizophrenia), Muree-Sauda (depression), Ishk (delusion of love); Nisyan (Organic mental disorder), Haziyan (paranoid state) and Malikholia-a-maraki (delirium). Psychotherapy was known as ilaj-l- Nafsani in Unani Medicine (Nizamie and Goyal, 2010). A Chinese text entitled The Yellow Emperor's Classic of Internal Medicine, written around 1000 BC, described symptoms of insanity, dementia, and seizures. Demonic or supernatural possession was often implicated as the cause of psychotic behaviours. (Kyziridis TC, 2005)

Since antiquity, up to 16th century persons with psychotic disorders and other forms of mental illness have been left to themselves, sent off in “ships of fools,” locked in cages, “flogged into reason,” chained, or simply killed, in some instances. Until the 1500s, the care of the insane in Europe—what little was offered—had been the responsibility of monks and nuns. Many social and historical changes converged in the 17th century (especially in England) to change this dark state of affairs for people with mental disorders. The institution of private madhouses for the care of the insane also began in this era and also involved physicians. Throughout the 1700s, physicians who doctored to the mentally ill in madhouses (both public and private) began to be recognized for their medical specialty and were called mad-doctors or lunatic-doctors in England and its colonies. William Battle of St. Luke’s Hospital in London, John Haslam of “Bedlam” in London, and William Cullen of Edinburgh became world-famous authorities through their written observations on madness. After 1801 it was the French who dominated the medical study of the mentally ill until mid-century, when the Germans began their domination of this field. Indeed, the devotion of the early French aliénistes (Pinel, Esquirol, and the members of the “Esquirol Circle”) to the study and classification of mental disorders directly led to the development of a distinct medical specialty for mental illness, which is now universally known as “psychiatry.” In 1801 French physician Philippe Pinel published his famous treatise on insanity l’aliénation mentale, or “mental alienation.” The first edition of Pinel’s Traité médico-philosophique sur l’aliénation mentale, ou la manie established him as the world’s leading authority on mental illness and helped to persuade the world that the mentally ill could be treated in a more humane manner through his philosophy of “moral treatment” (Noll R, 2009).
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2.3.1. Schizophrenia - Conceptual History

The current concept of schizophrenia is regarded as the consequence of a linear progress from different definitions concluding in the present. However, according to other school of thought the current view of schizophrenia is not the result of linear progression culminating in the present definition status in to one definition and one object of inquiry successively studied by various psychiatric groups but a patchwork made out of clinical features plucked from different definitions. The history of schizophrenia can be best described as the history of a set of research programmes running in parallel rather than serialism and each based on a different concept of disease, of mental symptom and of mind (Noll R 200?, Berrios GE et al 2003, Sadock BJ and Sadock VA 2010)

1800s: Psychiatry (and Schizophrenia) begins

- 1809 John Haslam of the Bethlem Royal Hospital in London and Philippe Pinel of the Salpêtrière asylum in Paris both produced expanded second editions of books on mental illness that had been published previously, they contain the first complete reports of what now known as schizophrenia in its “chronic” (or “Type II”) form. Haslam’s 1809 observations on Madness and Melancholy may be the first valid historical evidence in the English language for schizophrenia.

- 1852. Schizophrenia was first formally described by Belgian Psychiatrist Bénédict Augustin Morel, who called it démence précoce (Sadock B J and Sadock V A., 2010), literally "early dementia", described a distinct syndrome affecting teenagers and young adults The syndrome is characterized by bizarre behaviour and mental function, withdrawal and self neglect starting in adolescence.

- 1868- Kahlbaum’s Katatome Karl Ludwig Kahlbaum of Prussia published Die Gruppirung der psychischen Krankheiten (The Classification of Psychiatric Diseases). In this book, Kahlbaum described a class of progressively degenerating psychotic disorders that he grouped under the term “Vesania typical” (typical insanity). He was accompanied by his younger assistant, Ewald Hecker, and together they conducted a series of research studies on young psychotic patients that would eventuate in a major influence on the development of modern psychiatry Together Kahlbaum and Hecker were the first to describe and name a number of psychiatric syndromes including cyclothymia, dysthymia, paranoia, catatonia, and hebephrenia

- 1871. Ewald Hecker. He was the first researcher to describe enlarged cerebral ventricles in the postmortem examination of brains from deceased psychotic patients One of the classic subtypes of schizophrenia better known throughout the history of psychiatry as hebephrenia was first described by him in 1871

- 1891 Arnold Pick reported on a case of a psychotic disorder which he called Dementia Praecox.

- 1896: Emil Kraepelin, a German Psychiatrist, applied the term ‘dementia precox’ to a group of illnesses beginning in adolescence that ended in dementia. (Sadock BJ and Sadock VA, 2010)
1900s onwards

- 1911-Swiss psychiatrist Eugene Bleuler introduced the term schizophrenia. No signs or symptoms are pathognomonic, instead a cluster of characteristic findings indicate the diagnosis. He introduced the concept of fundamental symptoms (Grund symptome) called 'Four As': associational disturbances, affective disturbances, autism, and ambivalence. Influenced by his associate Carl Gustav Jung, Sigmund Freud and the psychoanalytic movement, Bleuler believed in the possibility of psychogenic or reactive triggers for schizophrenia, which Kraepelin did not allow.

- 1887 – 1967: Kurt Schneider contributed a description of first-rank symptoms, which, he stressed, were not specific for schizophrenia and were not to be rigidly applied but were useful for making diagnoses. He emphasized that in patients who showed no first-rank symptoms, the disorder could be diagnosed exclusively on the basis of second-rank symptoms and an otherwise typical clinical appearance. (Sadock B J and Sadock V A , 2007)

**Kurt Schneider Criteria for schizophrenia** (Sadock BJ and Sadock VA, 2007)

1. First-rank symptoms
   a. Audible thoughts
   b. Voices arguing or discussing or both
   c. Voices commenting
   d. Somatic passivity experiences
   e. Thought withdrawal and other experiences of influenced thought
   f. Thought broadcasting
   g. Delusional perceptions
   h. All other experiences involving volition made affects, and made impulses

2. Second-rank symptoms
   a. Other disorders of perception
   b. Sudden delusional ideas
   c. Perplexity
   d. Depressive and euphoric mood changes
   e. Feelings of emotional impoverishment
   f. and several others as well

   o Clinicians frequently ignore his warnings and sometimes see the absence of first-rank symptoms during a single interview as evidence that a person does not have schizophrenia

   o He included thought insertion/broadcast/withdrawal, made feelings/impulses/actions/somatic sensations (a type of delusion), third person auditory hallucinations (running commentary or arguments), delusional perception, and thought echo (echo de la pensee or gendankenlautwerden) – a type of hallucination
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- **1883-1969** Karl Jaspers, a psychiatrist and philosopher, played a major role in developing existential psychoanalysis. He was interested in the phenomenology of mental illness and the subjective feelings of patients with mental illness. His work paved the way toward trying to understand the psychological meaning of schizophrenic signs and symptoms such as delusions and hallucinations.

- **1970s** Advances in the technology to study biochemistry, brain function and structure, genetics, and the development of brain imaging techniques all converged to stimulate a biological renaissance in the study of schizophrenia and the psychotic disorders in the 1970s.

- **1980s, 1990s, and Beyond** The last two decades of the 20th century brought more scientific progress than the last 100 years combined in the understanding and treatment of schizophrenia and other psychotic disorders. There is no single environmental factor that has been strongly linked to the cause and development of schizophrenia. There is no objective medical test for diagnosing this disorder. No blood test or brain scan can confirm a diagnosis. The strongest evidence for a biological cause for schizophrenia seems to lie in the evidence provided in genetics studies. It is now known that genetics plays a key role in the cause and development of schizophrenia and bipolar disorder. Several candidates for the locus of the genes that cause schizophrenia are the subject of intense scrutiny.

First proposed by R. H. Murray in 1985 and D. R. Weinberger in 1986, the neurodevelopmental model claims that the causes of schizophrenia originate in subtle abnormalities that occur sometime during the early development of the nervous system of the fetus. This approach has sparked new research into a wide variety of old topics of schizophrenia research, such as childhood-onset schizophrenia. Schizophrenia does not seem to follow the pattern of being a neurodegenerative disease like Alzheimer's disease, so neurodevelopmental theories are prominent almost by default. Whether neurodevelopmental schizophrenia turns out to be the main illness or is found to be only one of several subtypes of schizophrenia remains to be seen.

The mode of genetic transmission remains a mystery, however, the National Institute of Mental Health Schizophrenia Genetics Initiative that began in 1989 is collecting and analyzing the DNA of persons with schizophrenia and their entire families in order to find a solution. Environmental factors still play an important role, too, in the development of the psychotic disorders, but no one knows what they are or how they interact with genes. Advances in brain imaging technology, neurochemistry, and neuropathology have produced sophisticated new models of schizophrenia based on the notion of disconnection between certain neural circuits or pathways in the brain. The prefrontal region of the frontal lobe and the temporal lobe are the two cortical regions most affected in schizophrenia. Subcortical structures such as the thalamus, a major relay center for messages traveling throughout the brain, and the hippocampus and cerebellum also have been implicated in schizophrenia (Noll R, 2009).
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Still, no one can dispute the fact that schizophrenia research will be one of the most fascinating areas of science as the new century unfolds.

2.4. Schizophrenia – Epidemiology, Etiopathology and Pathophysiology

2.4.1. Schizophrenia – Epidemiology and Risk Factors

A. Incidence and prevalence. It is found in all societies and in all geographic areas. Worldwide, 2 million new cases appear each year (Sadock BJ and Sadock VA, 2010). The details of prevalence are as mentioned in the introduction. In developed countries, schizophrenia is a chronic disease, causing impairment (neurocognitive, social, and occupational) that lasts a lifetime. In developing countries, schizophrenia follows a less severe course and has a better outcome. No one knows why this is so. (Noll R, 2009)

B. Gender and age. Equally prevalent between men and women. Usually onset is earlier in men. Peak age of onset is between 15 and 35 years (50% of cases occur before age 25). Onset before age 10 (called early-onset schizophrenia) or after age 45 (called late-onset schizophrenia) is uncommon (Sadock BJ and Sadock VA, 2010).

C. Infection and birth season. Persons born in winter are more likely to develop the disease than those born in spring or summer (applies to both Northern and Southern Hemispheres). Increased in babies born to mothers who have influenza during pregnancy (Sadock BJ and Sadock VA, 2010).

D. Race and religion. Jews are affected less often than Protestants and Catholics and prevalence is higher in nonwhite populations. (Sadock BJ and Sadock VA, 2010)

E. Medical and mental illness (comorbidity). Higher mortality rate from accidents and natural causes than in general population. Leading cause of death in schizophrenic patients is suicide (10%). Over 40% of schizophrenic patients abuse drugs and alcohol. Treatment with antipsychotic agents increases the risk of developing diabetes and the metabolic syndrome (Sadock BJ and Sadock VA, 2010).

F. Substance Abuse

Substance abuse is common in schizophrenia. The lifetime prevalence of any drug abuse (other than tobacco) is often greater than 50 percent. For all drugs of abuse (other than tobacco), abuse is associated with poorer function. In one population-based study, the lifetime prevalence of alcohol within schizophrenia was 40 percent. Alcohol abuse increases risk of hospitalization and, in some patients, may increase psychotic symptoms. People with schizophrenia have an increased prevalence of abuse of common street drugs. There has been particular interest in the association between cannabis and schizophrenia. Those reporting high levels of cannabis use (more than 50 occasions) were at sixfold increased risk of schizophrenia compared to nonusers. The use of amphetamines,
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cocaine, and similar drugs should raise particular concern because of their marked ability to increase psychotic symptoms. (Sadock BJ and Sadock VA, 2010)

**Nicotine.** Up to 90 percent of schizophrenic patients may be dependent on nicotine. Apart from smoking-associated mortality, nicotine decreases the blood concentrations of some antipsychotics. There are suggestions that the increased prevalence in smoking is due, at least in part, to brain abnormalities in nicotinic receptors. A specific polymorphism in a nicotinic receptor has been linked to genetic risk for schizophrenia. Nicotine administration appears to improve some cognitive impairments and Parkinsonism in schizophrenia, possibly because of nicotine-dependent activation of dopamine neurons. Recent studies have also demonstrated that nicotine may decrease positive symptoms such as hallucinations in schizophrenia patients by its effect on nicotinic receptors in the brain that reduce the perception of outside stimuli, especially noise. In that sense, smoking is a form of self-medication (Sadock BJ and Sadock VA, 2010)

**Socio economics.** More common among lower rather than higher socioeconomic groups; high prevalence among recent immigrants, most common in cities with over 1 million population. Direct and indirect costs resulting from schizophrenic illness in the United States are over 51 billion $ per year (Sadock BJ and Sadock VA, 2010)

2.4.2. Schizophrenia – Etiopathology

Owing to the heterogeneity of the symptomatic and prognostic presentations of schizophrenia, no single factor is considered causative. The stress diathesis model is most often used, which states that the person in whom schizophrenia develops has a specific biological vulnerability, or diathesis, that is triggered by stress and leads to schizophrenic symptoms. Stressors may be genetic, biological, and psychosocial or environmental. (Sadock BJ and Sadock VA, 2010)

**A. Genetic.** The rate of schizophrenia is increased in families with affected members. Both single-gene and polygenic theories of mode of transmission have been proposed. Although neither theory has been definitively substantiated, the polygenic theory appears to be more consistent with the presentation of schizophrenia. (Sadock BJ and Sadock VA, 2010)

1. Consanguinity. Incidence in families is higher than in the general population, and monozygotic (MZ) twin concordance is greater than dizygotic (DZ)

2. Adoption studies
   a. The prevalence of schizophrenia is greater in the biological parents of schizophrenic adoptees than in adoptive parents
   b. Monozygotic twins reared apart have the same concordance rate as twins reared together
   c. Rates of schizophrenia are not increased in children born to unaffected parents but raised by a schizophrenic parent
B. Infectious theory. Evidence for a slow virus etiology includes neuropathological changes consistent with past infection gliosis, glial scarring, and antiviral antibodies in the serum and cerebrospinal fluid (CSF) of some schizophrenic patients. Increased frequency of perinatal complications and seasonality of birth data also support an infectious theory (Sadock BJ and Sadock VA, 2010).

C. Psychosocial and Environmental Factors

1. Family factors. Patients whose families have high levels of expressed emotion (EE) have higher relapse rates than those whose families have low EE levels. EE has been defined as any overly involved intrusive behavior, be it hostile and critical or controlling and infantilizing. Relapse rates are better when family behavior is modified to lower EE. Most observers believe that family dysfunction is a consequence, rather than a cause of schizophrenia. (Sadock BJ and Sadock VA, 2010)

2. Other psychodynamic issues. Knowing what psychological and environmental stresses are most likely to trigger psychotic decompensation in a patient helps the clinician to address these issues supportively and in the process, helps the patient to feel and remain more in control. (Sadock BJ and Sadock VA, 2010)

D. Biological Factors

1) Dopamine hypothesis. The dopamine hypothesis for schizophrenia is the most fully developed of several hypotheses and is the basis for much of the rationale for drug therapy (Katzung BG, Masters SB & Trevor AJ, 2012). The original dopamine theory of schizophrenia was proposed by Carlson who was awarded a Nobel Prize in 2000 on the basis of indirect pharmacological evidence in humans and experimental animals (Rang HP et al, 2011). For more than 25 years, it has been observed that diseases or drugs that increase dopamine enhance or produce positive psychotic symptoms, whereas drugs that decrease dopamine decrease or stop positive symptoms (Stahl SM, 2008). Although dopamine serves as a precursor of norepinephrine and epinephrine, it does not have noticeable sympathomimetic function.
**Dopamine and Its Receptor Family in nervous system:**

There are currently five types of dopamine receptors identified in the human nervous system, D1 to D5. All belong to the family of G-protein-coupled transmembrane receptors. The dopamine receptors’ signal transduction mechanisms (linked via adenylyl cyclase and/or phospholipid hydrolysis to the control of potassium and calcium channels, arachidonic acid release, etc) are similar to those of other such receptors. A
key component in the signal transduction pathway is the protein DARPP-32 (32-kDa dopamine- and cAMP-regulated phosphoprotein). When intracellular cAMP is increased through activation of D1 receptors, and protein kinase A, DARPP-32 is phosphorylated. Phosphorylated DARPP-32 acts as an inhibitor of protein phosphatases such as protein phosphatase-1 and calcineurin, thus acting in concert with protein kinases and favouring protein phosphorylation—effectively an amplifying mechanism (Rang HP et al., 2011).

D1 and D5 receptors are similar in that they both stimulate the formation of cAMP by activation of a stimulatory G-coupled protein. D1 and D5 are therefore known as D1-like receptors. D2 to D4 receptors activate an inhibitory G-protein, thereby inhibiting the formation of cAMP. They are collectively known as D2-like receptors. D2 receptors are more ubiquitous than D3 or D4 receptors. D3 receptors are differentially situated in the nucleus accumbens (one of the septal nuclei in the limbic system) and D4 receptors are especially concentrated in the frontal cortex. Activation of D2 receptors opposes the effect of D1 receptor activation. (Rang HP et al., 2011)

Schizophrenic symptoms may result from increased limbic dopamine activity (positive symptoms) and decreased frontal dopamine activity (negative symptoms). Dopaminergic pathology may be secondary to abnormal receptor number or sensitivity or abnormal dopamine release (too much or too little). The theory is based on psychotogenic effects of drugs that increase dopamine levels (e.g., amphetamines, cocaine) and the antipsychotic effects of dopamine receptor antagonists (e.g., haloperidol). Dopamine receptors D1 through D5 have been identified. The D1 receptor may play a role in negative symptoms. Specific D3 and D4 receptor agonist and antagonist drugs are under development. Levels of the dopamine metabolite homovanillic acid may correlate with the severity and potential treatment responsiveness of psychotic symptoms. Limitations of the theory include the responsiveness of all types of psychoses to dopamine blocking agents, which implicates dopaminergic abnormalities in psychoses of multiple causes. The complex interplay of different neurotransmitter systems, including serotonin-dopamine interactions, amino acid neurotransmitters on monoamine render single-neurotransmitter theories incomplete (Sadock BJ and Sadock VA, 2010).

There are Four Key Dopaminergic Neuronal Pathways in the Brain: (Stahl SM, 2008)

a) Mesolimbic Dopamine Pathway: It projects from dopaminergic cell bodies in the ventral tegmental area (VTA) of the brainstem to axon terminals in limbic areas of the brain, such as the nucleus accumbens. This pathway is thought to have an important role in emotional behaviors, especially auditory hallucinations but also delusions and thought disorder. This pathway is also involved in pleasure, reward, and reinforcing behavior and many drugs of abuse interact here.
b) **Mesocortical Dopamine Pathway**: Its cell bodies arise in the ventral tegmental area (VTA) of the brainstem, near the cell bodies for the dopamine neurons of the mesolimbic dopamine pathway. The role of the mesocortical dopamine pathway in mediating negative and/or cognitive symptoms of schizophrenia is still a matter of debate.

c) **Nigrostriatal Dopamine Pathway**: It projects from dopaminergic cell bodies in the substantia nigra of the brainstem via axons terminating in the basal ganglia or striatum. The nigrostriatal dopamine pathway is a part of the extrapyramidal nervous system and controls motor movements. Deficiencies in dopamine in this pathway cause movement disorders, including Parkinson's disease, which is characterized by rigidity, akinesia or bradykinesia (i.e., lack of movement or slowing of movement), and tremor. Dopamine deficiency in the basal ganglia also can produce akathisia (a type of restlessness) and dystonia (twisting movements, especially of the face and neck). These movement disorders can be replicated by drugs that block dopamine 2 receptors in this pathway (drug-induced movement disorders).

d) **Tuberoinfundibular or Tuberohypophyseal Dopamine Pathway**: The dopamine neurons that project from the hypothalamus to the anterior pituitary are known as the tuberoinfundibular dopamine pathway. Normally, these neurons are active and inhibit prolactin release. If the functioning of tuberoinfundibular dopamine neurons is disrupted by lesions or drugs, prolactin levels can also rise. Elevated prolactin levels are associated with galactorrhea, amenorrhea and possibly other problems, such as sexual dysfunction. Such problems can occur after treatment with many antipsychotic drugs that block dopamine 2 receptors

2) **Norepinephrine hypothesis.** Increased norepinephrine levels in schizophrenia lead to increased sensitization to sensory input (Sadock BJ and Sadock VA, 2010)

3) **γ-Amino butyric acid (GABA) hypothesis.** Decreased GABA activity results in increased dopamine activity. (Sadock BJ and Sadock VA, 2010)

4) **Serotonin hypothesis.** Interest in 5-HT (5-hydroxytryptamine) as a possible CNS transmitter dates from 1953, when Gaddum found that lysergic acid diethylamide (LSD), a drug known to be a powerful hallucinogen, acted as a 5-HT antagonist on peripheral tissues, and suggested that its central effects might also be related to this action. Even though brain accounts for only about 1% of the total body content, 5-HT is an important CNS transmitter. 5-HT is involved in various physiological processes including sleep, appetite, thermoregulation and pain perception as well as in disorders such as migraine, depression, anxiety, obsessive compulsive disorders, schizophrenia and drug abuse (Rang HP et al, 2011)

Serotonin metabolism apparently is abnormal in some chronically schizophrenic patients with both hyperserotoninemia and hyperserotoninemia being reported. Specifics antagonism at the serotonin 5-HT2 receptor has been emphasized as important in reducing psychotic symptoms and the development of movement disorders related to D2 dopaminergic antagonism. Research on mood disorders has implicated
serotonin activity in suicidal and impulsive behaviour with schizophrenic can also exhibit (Sadock BJ and Sadock VA, 2010)

**Serotonin (5-HT) and Its Receptor Family in nervous system:** (Rang HP et al, 2011)

- 5-HT neurons are concentrated in the midline raphe nuclei in the brain stem projecting diffusely to the cortex, limbic system, hypothalamus and spinal cord, similar to the noradrenergic projections.

- 5-HT can exert inhibitory or excitatory effects on individual neurons, acting either presynaptically or postsynaptically

- The main receptor subtypes in the CNS are 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{2A}$, 5-HT$_{2C}$ and 5-HT$_{3}$. Associations of behavioural and physiological functions with these receptors have been partly worked out. Other receptor types (5-HT$_{4,7}$) also occur in the central nervous system, but less is known about their function. Except for 5-HT$_{3}$, which is a ligand-gated cation channel receptor, all rest of the 5-HT receptor subtypes are G-protein-coupled receptors

- 5-HT Neuronal Pathways in CNS The distribution of 5-HT-containing neurons resembles that of noradrenergic neurons. The cell bodies are grouped in the pons and upper medulla, close to the midline (raphe), and are often referred to as raphe nuclei. The rostrally situated nuclei project via the medial forebrain bundle to many parts of the cortex, hippocampus, basal ganglia, limbic system and hypothalamus. The caudally situated cells project to the cerebellum, medulla and spinal cord.

- Functions associated with 5-HT pathways in CNS include
  - various behavioural responses (e.g. hallucinatory behaviour, 'wet dog shakes')
  - control of mood and emotion
  - control of sleep/wakefulness
  - feeding behaviour
  - control of sensory pathways, including nociception
  - control of body temperature
  - vomiting

- Serotonin Dopamine Antagonist (SDA) antipsychotics (e.g. clozapine, olanzapine, quetiapine, risperidone, paliperidone, ziprasidone, iloperidone, aripiprazole, asenapine) owe their efficacy partly to an action on 5-HT receptors

5)Glutamate hypothesis. Hypofunction of the glutamate N-methyl-D aspartate (NMDA)-type receptor is theorized to cause both positive and negative symptoms of schizophrenia based on the observed psychotogenic effects of the NMDA antagonists phencyclidine and ketamine in addition to the observed therapeutic effects (in research settings) of the NMDA agonists glycine and D-cycloserine (Sadock BJ and Sadock VA, 2010)
Glutamate and related excitatory amino acids activate both ionotropic (ligand-gated cation channels) and metabotropic (G-protein-coupled) receptors. On the basis of studies with selective agonists and antagonists, three main subtypes of ionotropic receptors for glutamate can be distinguished: NMDA, AMPA and Kainate receptors, named originally according to their specific agonists. NMDA receptors are assembled from seven types of subunit (GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A, GluN3B). The subunits comprising AMPA receptors (GluA1-4) and kainate receptors (GluK1-3), are closely related to, but distinct from, GluN subunits. Inotropic receptors comprising different subunits can have different pharmacological and physiological characteristics. There are eight different metabotropic glutamate receptors (mGlu1-8) which are unusual in showing no sequence homology with other G-protein-coupled receptors. In general, it appears that NMDA and mGlu receptors play a particular role in long-term adaptive and pathological changes in the brain, and are of particular interest as potential drug targets (Rang HP et al., 2011).

Glutamatergic neurons and GABAergic neurons play complex roles in controlling the level of neuronal activity in both the mesocortical and the mesolimbic dopaminergic pathways. NMDA receptor hypofunction is thought to reduce the level of activity in mesocortical dopaminergic neurons. This would result in a decrease in dopamine release in the prefrontal cortex and thus give rise to negative symptoms of schizophrenia. On the other hand, NMDA receptor hypofunction is thought to enhance activity in the mesolimbic dopaminergic pathway, perhaps because in this pathway the important NMDA receptors are those located on GABAergic interneurons. Thus NMDA receptor hypofunction would result in reduced GABAergic inhibition (dissipation) of mesolimbic dopaminergic neurons and thus give rise to enhanced dopamine release in limbic areas such as the nucleus accumbens, resulting in the production of positive symptoms (Rang HP et al., 2011).

Given the evidence that schizophrenic symptoms may be due to a reduction in NMDA receptor function, efforts have been made to develop new drugs to enhance NMDA receptor function but not to a level where it becomes neurotoxic. This could be achieved by activating the facilitatory glycine site on the NMDA receptor with an agonist or by raising extracellular glycine levels by inhibiting the GlyT1 transporter. AMPAkines are the agents that allosterically enhance the action of glutamate at the AMPA receptor, by enhancing glutamate-induced neuronal depolarisation, can potentiate NMDA responses. Paradoxically, reducing glutamate release by activating presynaptic mGluR2/3 autoreceptors may result in a compensatory upregulation of NMDA receptors which also might be beneficial. This provides a novel target for the development of new antipsychotic drugs. Other glutamate pathways thought to be involved in schizophrenia are the corticostriatal, thalamocortical, corticothalamic and cortico-brain stem pathways (Rang HP et al., 2011).

Pharmacological evidence is generally consistent with dopamine dysregulation and glutamate underactivity hypotheses supported by biochemical findings, clinical efficacy and imaging studies. (Rang HP et al., 2011)
E. Neurodevelopmental theories. There is evidence of abnormal neuronal migration during the second trimester of fetal development. Abnormal neurons' functioning may lead to the emergence of symptoms during adolescence. (Sadock BJ and Sadock VA, 2010)

![Grey-matter volume changes during normal development](image)

**Fig. 5. Cortical Developmental Changes in Normal and Schizophrenic Brain (Ref.: Insel T.R., 2012)**

a. Normal cortical development involves proliferation, migration, arborization (circuit formation) and myelination, with the first two processes occurring mostly during prenatal life and the latter two continuing through the first two postnatal decades. The combined effects of pruning of the neuronal arbor and myelin deposition are thought to account for the progressive reduction of grey-matter volume observed with longitudinal neuroimaging. Beneath this observed overall reduction, local changes are far more complex. Data from human and non-human primate brain indicate increases in inhibitory and decreases in excitatory synaptic strength occurring in prefrontal cortex throughout adolescence and early adulthood, during the period of prodrome and emergence of psychosis. b. The trajectory in children developing schizophrenia could include reduced elaboration of inhibitory pathways and excessive pruning of excitatory pathways leading to altered excitatory–inhibitory balance in the prefrontal cortex. Reduced myelination would alter connectivity. Although some data support each of these possible neurodevelopmental mechanisms for schizophrenia, none has been proven to cause the syndrome. Detection of prodromal neurodevelopmental changes could permit early intervention with potential prevention or preemption of psychosis.
In most medical disorders what is known about epidemiology maps directly onto theories of pathogenesis. This has not been the case for schizophrenia. However, now it is known that the main risk factors for schizophrenia and that dopamine-driven dysfunction of the process of attribution of salience underlies some of the positive symptoms of psychosis, the way is open to attempt to link the two, as outlined in above-given figure. Of course, it is likely that there are many steps in between risk factors and the dopamine system, involving, for example, GABA and glutamate systems. However, the evidence that is briefly mentioned suggests that there is merit in setting up hypotheses to test the relationship between identified risk factors and striatal dopamine regulation. (Gattaz WF & Busatto G, 2009)

F. Neurodegenerative theories (Fig.7):
Factors such as structural abnormalities in the brains of schizophrenics and progression of the disease—absence of symptoms in early childhood, the likelihood of positive symptoms becoming apparent before negative symptoms, progressive worsening, reduced responsiveness to drugs with time and the development of dementia—all indicate the involvement of ongoing neurodegeneration in the disease. The causes of such neurodegeneration are unclear at present but may involve glutamate-induced excitotoxicity. (Rang HP et al., 2011)
2.4.3. Schizophrenia - Pathophysiology

A. Neuropathology

While there are no structural or functional brain changes specific to schizophrenia or other psychotic disorders, a number of abnormalities are reported. Changes noted include decreased number of neurons, increased gliosis and disorganization of neuronal architecture; Degeneration in the limbic system especially the amygdala, hippocampus and cingulate cortex and in the basal ganglia, especially the substantia nigra and dorsolateral prefrontal cortex. Abnormal functioning in basal ganglia and cerebellum may account for movement disorders in schizophrenic patients (Sadock BJ and Sadock VA, 2010)

B. Brain imaging (Sadock BJ and Sadock VA, 2010)

1. Computed tomography (CT). Cortical atrophy in 10% to 35% of patients, enlargement of the lateral and third ventricle in 10% to 50% of patients, atrophy of the cerebellar vermis and decreased radiodensity of brain parenchyma. Abnormal CT findings may correlate with the presence of negative symptoms (e.g. flattened affect, social withdrawal psychomotor retardation, lack of motivation, neuropsychiatric impairment, increased frequency of extrapyramidal symptoms resulting from antipsychotic medications and poor premorbid history).

2. Magnetic resonance imaging (MRI). Ventricles in MZ twins with schizophrenia are larger than those of unaffected siblings. Reduced volume of hippocampus, amygdala, and parahippocampal gyrus. Reduced limbic volume correlating with disease severity


4. Positron emission tomography (PET). In some patients decreased frontal and parietal lobe metabolism, relatively high rate of posterior metabolism and abnormal laterality

5. Cerebral blood flow (CBF). In some patients' decreased resting levels of frontal blood flow; increased parietal blood flow, and decreased whole-brain blood flow. When PET and CBF studies are considered together with CT findings, dysfunction of the frontal lobe is most clearly implicated. Frontal lobe dysfunction may be secondary, however, to disease elsewhere in the brain.

C. Electrophysiology (Winterer, G and McCarley, R. W., 2011)

1. P50 sensory gating deficits. Following auditory stimulus schizophrenia patients fail to gate a subsequent stimulus that follows closely (within the normal 50 msec suppression)

2. Reduced P300 evoked response potential (ERP) [oddball deficit paradigm]. Schizophrenia patients fail to respond to an odd ball stimulus administered during a series of otherwise identical stimuli.

3. Prepulse Inhibition (PPI) Paradigm.

D. Physical findings (Sadock BJ and Sadock VA, 2010)

Minor (soft) neurological findings occur in 50% to 100% of patients. Increased prevalence of primitive
reflexes (e.g. grasp reflex), abnormal stereognosis and two-point discrimination, and dysdiadochokinesia (impairment in ability to perform rapidly alternating movements). Paroxysmal saccadic eye movements (inability to follow object through space with smooth eye movements) occur in 50% to 80% of schizophrenic patients and in 40% to 45% of first-degree relatives of schizophrenic patients (compared with 8% to 10% prevalence in nonschizophrenic persons). This may be a neurophysiological marker of a vulnerability to schizophrenia. Resting heart rates have been found to be higher in schizophrenic patients than in controls and may reflect a hyperaroused state.

2.4.4. Psychodynamic Factors in Schizophrenia (Sadock BJ and Sadock VA, 2010)

Understanding a patient’s dynamics (or psychological conflicts and issues) is critical for complete understanding of the symbolic meaning of symptoms. A patient’s internal experience is usually one of confusion and overwhelming sensory input, and defense mechanisms are the ego’s attempt to deal with powerful affects.

Three major primitive defenses interfere with reality testing, (1) psychotic projection-attributing inner sensations of aggression, sexuality chaos and confusion to the outside world, as opposed to recognizing them as emanating from within: boundaries between inner and outer experience are confused, projection is the major defense underlying paranoid delusions (2) reaction formation-turning a disturbing idea or impulse into its opposite and (3) psychotic denial-transforming confusing stimuli into delusions and hallucinations.

2.4.5. Integrating the Epidemiology and Pathogenesis of Schizophrenia:
(Ref Murray, RM, Di Forti M and Howes O, 2009)

Research into schizophrenia has proceeded in a patchwork manner as if isolated portions of a giant jigsaw were being completed with little thought as to how these might contribute to the whole picture. For example, investigations into the two major pathogenic theories of schizophrenia, namely the dopamine hypothesis and the neurodevelopmental hypothesis, proceeded for many years in parallel with little crosstalk. Only recently have there been attempts to integrate the two theories. Murray et al (2008) concluded that dopamine dysregulation is the final step in a complex developmental cascade that starts early in life and ends with the onset of full-blown psychosis.

The neurodevelopmental hypothesis originally supposed that variants of developmental genes interacted with early neurological insults to produce developmental deviance and ultimately schizophrenia. As a result of epidemiological studies this hypothesis has been modified to include the pathogenic effects of abuse of certain drugs and also of chronic social adversity; therefore, it is perhaps now more appropriately termed the developmental hypothesis (Howes et al, 2004). Unfortunately, there has been no such productive interchange between epidemiologists and dopamine theorists. Given the central role that dopamine
dysregulation appears to play in the proximal pathogenesis of psychosis (Howes and Kapur, 2009), one inevitably must consider the causes of this dysregulation. Di Forti et al (2007) have elsewhere briefly outlined some of the evidence that various established risk factors for schizophrenia impact on the dopamine system. A logical extension of such reasoning is to consider whether the epidemiology of schizophrenia may be explained on the basis of what is known about the pathophysiology of dopamine.

2.4.6. Striatal Dopamine as the 'Wind of Psychotic Fire' (Murray RM et al, 2009)

The 'classical' dopamine hypothesis of schizophrenia was proposed over 30 years ago and states that schizophrenia is associated with an exaggerated dopaminergic function in the central nervous system (Snyder, 1976). It is now known that it is a synaptic excess of dopamine: patients with schizophrenia show elevated baseline striatal availability of dopamine (Abi-Dargham, 2004, Howes et al., 2007) and increased release of dopamine in the striatum following amphetamine challenge (Laruelle et al., 1996; Breier et al., 1997; Abi-Dargham et al., 1998; Laruelle and Abi-Dargham, 1999a, b) Furthermore, the degree of dopamine release is directly related to the severity of symptoms, particularly psychotic symptoms (Laruelle et al., 1999b)

Recently understanding has developed about how excessive release of dopamine facilitates the development of the classic positive symptoms of psychosis, hallucinations, and delusions. Building on the evidence that dopamine normally mediates the attachment of salience to ideas and objects, Kapur et al (2005) proposed that heightened dopaminergic neurotransmission leads to aberrant assignment of salience to normal external and internal stimuli and that delusions arise from attempts to explain this. Until recently this remained only a theory. However, now Murray GK et al. (2008b) have shown that first-episode psychotic patients show less ability than controls to distinguish between motivationally salient stimuli as opposed to neutral stimuli, i.e., they showed rapid reactivity even to stimuli that predicted no reward. Furthermore, fMRI demonstrated that the patients showed smaller differences than controls in midbrain activation in response to stimuli that either predicted the possibility of reward or did not. Thus the patients showed both behavioral and physiological evidence of abnormality in dopamine-based reinforcement learning and provide empirical support for Kapur’s theory

When does this dopaminergic dysregulation develop? It is known that it occurs before the onset of frank psychosis and that there is excess release of dopamine from the striatum in individuals who are at ultra high risk of psychosis, as well as those experiencing their first psychotic episode (Howes et al., 2009) This suggests that, somewhere around their late teens, patients develop an abnormality of the dopamine system such that there is an exaggerated release of dopamine to normal stimuli (Cited by Noll, 2009)
2.5. Diagnosis of Schizophrenia

Although schizophrenia is the commonest and best known psychotic illness, it is not synonymous with psychosis but is just one of many causes of psychosis (Stahl SM, 2008). According to DSM-IV manual, schizophrenia is diagnosed when the patient presents with a combination of positive (delusions and hallucinations) and negative symptoms, which have been present for at least 6 months and have resulted in significant dysfunction. It is also accepted that disorganized speech/behaviour and/or catatonic symptoms, when combined with other positive or negative symptoms, can count towards a diagnosis of schizophrenia. Schizophrenia is a diagnosis of exclusion; in other words, it is required that there are no other medical, psychiatric, or substance-induced conditions that would explain the patient’s diagnosis better than schizophrenia (American Psychiatric Association, 1994) (Stefan M, Travis M & Murray RM, 2002). Despite the advent of variety of operational definitions, categorical definitions of schizophrenia vary in their cut-off points on a theoretical continuum. There is substantial overlap between diagnostic systems and significant proportion of patients fulfill criteria in all systems (Sadock BJ and Sadock VA, 2010).

2.5.1. Schizophrenia – Diagnosis, Signs and Symptoms:

Schizophrenia is a disorder whose diagnosis is based on observation and description of the patient. Abnormalities are often present on most components of the mental status examination. There are no pathognomonic signs or symptoms (Sadock BJ and Sadock VA, 2010).

Five Symptom Dimensions in schizophrenia (Stahl SM, 2008)

Although not recognized formally as part of the diagnostic criteria for schizophrenia, numerous studies subcategorize the symptoms of this illness (as well as symptoms of some other disorders) into five basic symptoms dimensions: positive symptoms, negative symptoms, cognitive symptoms, aggressive/hostile symptoms, and depressive/anxious symptoms. Several illnesses other than schizophrenia share these symptoms dimensions as well.

a) Positive Symptoms

Positive symptoms seem to reflect an excess of normal functions. Disorders in addition to schizophrenia that can have positive symptoms include bipolar disorder, schizoaffective disorder, psychotic depression, Alzheimer’s disease.
b) Negative Symptoms

Negative symptoms commonly are considered a reduction in normal functions in schizophrenia.

Table 1. Positive and Negative Psychotic Symptoms (Ref. Sadock BJ and Sadock VA, 2010 and Stahl SM, 2008)

<table>
<thead>
<tr>
<th>Positive Symptoms</th>
<th>Negative Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>Affective flattening (Blunted affect)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>(reduction in the range and</td>
</tr>
<tr>
<td></td>
<td>intensity of emotional expression)</td>
</tr>
<tr>
<td>Distortions or</td>
<td>Alogia (restrictions in fluency and</td>
</tr>
<tr>
<td>exaggerations in</td>
<td>productivity of thought and speech)</td>
</tr>
<tr>
<td>language and</td>
<td>Avolition (restrictions in initiation of</td>
</tr>
<tr>
<td>communication</td>
<td>goal-directed behavior)</td>
</tr>
<tr>
<td>Disorganized</td>
<td>Anhedonia (lack of pleasure)</td>
</tr>
<tr>
<td>speech</td>
<td>Apathetic Social Withdrawal</td>
</tr>
<tr>
<td>Disorganized</td>
<td>Attentional impairment</td>
</tr>
<tr>
<td>behaviour</td>
<td>Emotional withdrawal</td>
</tr>
<tr>
<td>Catatonic</td>
<td>Passivity</td>
</tr>
<tr>
<td>behavior</td>
<td>Lack of spontaneity</td>
</tr>
<tr>
<td>Agitation</td>
<td>Poor rapport</td>
</tr>
<tr>
<td></td>
<td>Difficulty in abstract thinking</td>
</tr>
<tr>
<td></td>
<td>Stereotyped thinking</td>
</tr>
</tbody>
</table>

C) Cognitive Symptoms

Cognitive symptoms refer to the difficulties with concentration and memory. These can include:

1. Disorganized thinking
2. Slow thinking
3. Difficulty understanding
4. Poor concentration
5. Poor memory
6. Difficulty expressing thoughts
7. Difficulty integrating thoughts, feelings, and behavior

(The history of schizophrenia url: http://www.schizophrenia.com/history.htm Accessed 8 July 2012)

Cognitive symptoms of schizophrenia and other illnesses of which psychosis may be an associated feature can overlap with negative symptoms. They include specifically the thought disorder of schizophrenia and the sometimes odd use of language, including incoherence, loose associations, and neologisms. Impaired attention and impaired information processing are other specific cognitive impairments associated with schizophrenia. In fact, the most common and the most severe of the cognitive impairments in schizophrenia can include impaired verbal fluency (ability to produce spontaneous speech), problems with serial learning (of a list of items or a sequence of events), and impairment in vigilance for executive functioning (problems with sustaining and focusing attention, concentrating, prioritizing, and modulating behavior based on social cues). Schizophrenia is certainly not the only disorder with such impairments in cognition. Autism, post-stroke dementia, Alzheimer's disease, and many other organic dementias (parkinsonian/Lewy body...
dementia, frontotemporal/Pick's dementia, etc.) are also associated with some cognitive dysfunctions similar to those seen in schizophrenia.

d) Aggressive and Hostile Symptoms

Aggressive and hostile symptoms can overlap with positive symptoms but specifically emphasize problems in impulse control. They include overt hostility, such as verbal or physical abusiveness or even assault. Such symptoms also include self-injurious behaviors, including suicide and arson or other property damage. Other types of impulsiveness, such as sexual acting out, are also in this category of aggressive and hostile symptoms. Although aggressive symptoms are common in schizophrenia, they are far from unique to this condition. Thus, these same symptoms are frequently associated with bipolar disorder, childhood psychosis, borderline personality disorder, drug abuse, Alzheimer and other dementias, attention deficit hyperactivity disorder, conduct disorders in children, and many others (Stahl SM, 2008).

e) Depressive and Anxious Symptoms

Depressive and anxious symptoms are frequently associated with schizophrenia, but this does not necessarily mean that they fulfill the diagnostic criteria for a comorbid anxiety or affective disorder. Nevertheless, depressed mood, anxious mood, guilt, tension, irritability, and worry frequently accompany schizophrenia. These various symptoms are also prominent features of major depressive disorder, psychotic depression, bipolar disorder, schizoaffective disorder, organic dementias, and childhood. (Stahl SM, 2008)

Other frequent noticeable features of schizophrenia are listed below: (Sadock BJ and Sadock VA, 2010)

1. Overall functioning - Level of functioning declines or fails to achieve the expected level.
2. Thought content - Abnormal (e.g., delusions, ideas of reference, poverty of content). Delusions and hallucinations are not necessary to make the diagnosis if other signs and symptoms are present.
3. Form of thought - Illogical (e.g., derailment, loosening of associations, incoherence, circumstantiality, tangentiality, overinclusiveness, neologisms, blocking, Echolalia-all incorporated as a thought disorder).
4. Perception - Distorted (e.g., hallucinations: visual olfactory, tactile and most frequently auditory).
5. Affect - Abnormal (e.g., flat, blunted, silly, labile, inappropriate).
6. Sense of self - Impaired (e.g., loss of ego boundaries, gender confusion, inability to distinguish internal from external reality).
7. Volition - Altered (e.g., inadequate drive or motivation and marked ambivalence).
8. Interpersonal Functioning - Impaired (e.g., social withdrawal and emotional detachment, aggressiveness, sexual inappropriateness).
9. Psychomotor behaviour - Abnormal or changed (e.g., agitation versus withdrawal, grimacing, posturing, rituals, catatonia).
Psychotic Symptoms – In Brief:

Delusions – These are false beliefs strongly held in spite of invalidating evidence, especially as a symptom of mental illness for example,

1. Paranoid delusions, or delusions of persecution, for example believing that people are "out to get" you, or the thought that people are doing things when there is no external evidence that such things are taking place.

2. Delusions of reference - when things in the environment seem to be directly related to the person even though they are not. For example it may seem to the person as if people are talking about him/her or special personal messages are being communicated to him/her through the TV, radio, or other media.

3. Somatic Delusions are false beliefs about the body - for example that a terrible physical illness exists or that something foreign is inside or passing through his/her body.

4. Delusions of grandeur - for example when a person believes that he/she is very special or have special powers or abilities. An example of a grandiose delusion is thinking he/she is a famous rock star.

Hallucinations - Hallucinations can take a number of different forms - they can be.

1. Visual - seeing things that are not there or that other people cannot see,

2. Auditory - hearing voices that other people can't hear,

3. Tactile - feeling things that other people don't feel or something touching the skin that isn't there.

4. Olfactory - smelling things that other people cannot smell, or not smelling the same thing that other people do smell.

5. Gustatory experiences - tasting things that isn't there.

Disorganized speech/thinking, also described as “thought disorder” or “loosening of associations,” is a key aspect of schizophrenia. Disorganized thinking is usually assessed primarily based on the person’s speech. Therefore, tangential, loosely associated, or incoherent speech severe enough to substantially impair effective communication is used as an indicator of thought disorder by the DSM-IV criteria.

Grossly disorganized behavior includes difficulty in goal-directed behavior (leading to difficulties in activities in daily living), unpredictable agitation or silliness, social disinhibition, or behaviors that are bizarre to onlookers. Their purposelessness distinguishes them from unusual behavior prompted by delusional beliefs.

Catatonic behaviors are characterized by a marked decrease in reaction to the immediate surrounding environment, sometimes taking the form of motionless and apparent unawareness, rigid or bizarre postures, or aimless excess motor activity.

(Ref: The history of schizophrenia url http://www.schizophrenia.com/history.htm Accessed 8 July 2012)
2.5.2. Laboratory and Psychological Tests (Sadock BJ and Sadock VA, 2010)

A. EEG - Most schizophrenic patients have normal EEG findings but some have decreased alpha and increased theta and delta activity, paroxysmal abnormalities, and increased sensitivity to activation procedures (e.g., sleep deprivation).

B. Evoked potential studies - Initial hypersensitivity to sensory stimulation with later compensatory blunting of information processing at higher cortical levels.

C. Immunological studies - In some patients atypical lymphocytes and decreased numbers of natural killer cells.

D. Endocrinological studies - In some patients, decreased levels of luteinizing hormone and follicle-stimulating hormone diminished release of prolactin and growth hormone following stimulation by gonadotropin-releasing hormone or thyrotropin-releasing hormone.

E. Neurophysiological testing - Thematic apperception test and Rorschach test usually reveal bizarre responses. When compared with the parents of normal controls, the parents of schizophrenic patients show more deviation from normal values in projective tests (may be a consequence of living with schizophrenic family member). Halstead Reitan battery reveals impaired attention and intelligence, decreased retention time and disturbed problem-solving ability in approximately 20% to 35% of patients. Schizophrenic patients have lower IQs when compared with non-schizophrenic patients, although the range of IQ scores is wide. Decline in IQ occurs with progression of the illness.

2.5.3. Schizophrenia - Differential Diagnosis (Sadock BJ and Sadock VA, 2010)

A. Medical and neurological disorders - Present with impaired memory, orientation and cognition; visual hallucinations; signs of CNS damage. Many neurological and medical disorders can present with symptoms identical to those of schizophrenia including substance intoxication (e.g. cocaine, phencyclidine) and substance-induced disorder. CNS infections (e.g. herpes encephalitis), vascular...
disorders (e.g. systemic lupus erythematosus), complex partial seizures (e.g. temporal lobe epilepsy) and degenerative disease (e.g. Huntington’s disease).

B. Schizophreniform disorder - Symptoms may be identical to those of schizophrenia, but last for less than 6 months. Also deterioration is less pronounced and the prognosis is better.

C. Brief psychotic disorder - Symptoms last less than 1 month and proceed from a clearly identifiable psychosocial stress.

D. Mood disorders - Both manic episodes and major depressive episodes of bipolar disorder and major depressive disorder may present with psychotic symptoms. The differential diagnosis is particularly important because of the availability of specific and effective treatments for the mood disorders. Also, if hallucinations and delusions are present in a mood disorder, they develop in the context of the mood disturbance and do not persist. Other factors that help differentiate mood disorder from schizophrenia include family history, premorbid history, course (e.g., age at onset), prognosis (e.g. absence of residual deterioration following the psychotic episode) and response to treatment. Patients may experience post-psychotic depressive disorder of schizophrenia (i.e. a major depressive episode occurring during the residual phase of schizophrenia). True depression in these patients must be differentiated from medication induced adverse effects such as sedation, akinesia and flattening of affect.

E. Schizoaffective disorder - Mood symptoms develop concurrently with symptoms of schizophrenia, but delusions or hallucinations must be present for 2 weeks in the absence of prominent mood symptoms during some phase of the illness. The prognosis of this disorder is better than that expected for schizophrenia and worse than that for mood disorders.

F. Psychotic disorder not otherwise specified - An atypical psychosis with a confining clinical feature (e.g. persistent auditory hallucinations as the chief symptom, culture-bound psychoses)

G. Delusional disorders - Nonbizarre, systematized delusions that last at least 6 months in the context of an intact, relatively well-functioning personality in the absence of prominent hallucinations or other schizophrenic symptoms. Onset is in middle to late adult life.

H. Personality disorders - Generally no psychotic symptoms. But if present they tend to be transient and not prominent. The most important personality disorders in this differential diagnosis are schizotypal, schizoid, borderline and paranoid.

I. Fictitious disorder and malingering - No laboratory test or biological marker can objectively confirm the diagnosis of schizophrenia. Schizophrenic symptoms are therefore possible to feign for either clear secondary (malingering) or deep psychological motivations (factitious disorder).

J. Pervasive developmental disorders - Pervasive developmental disorders (e.g. autistic disorder) are usually recognized before 3 years of age. Although behavior may be bizarre and deteriorated, no delusions, hallucinations or clear formal thought disorder is present (e.g. loosening of associations).

K. Mental retardation - Intellectual, behavioral, and mood disturbances that suggest schizophrenia. However, mental retardation involves no overt psychotic symptoms and involves a constant level of
functioning rather than deterioration. If psychotic symptoms are present a diagnosis of schizophrenia may be made concurrent.

L. Shared cultural beliefs. Seemingly odd beliefs shared and accepted by a cultural group are not considered psychotic.

2.6. Types of Schizophrenia (Sadock BJ and Sadock VA, 2010)

A. Paranoid
1. Characterized mainly by the presence of delusions of persecution or grandeur.
2. Frequent auditory hallucinations related to a single theme. Usually persecutory.
3. Patients typically are tense. Suspicious, guarded, reserved and sometimes hostile or aggressive.
4. None of the following, incoherence, loosening of associations, flat or grossly inappropriate affect, catatonic behavior, grossly disorganized behavior. Intelligence remains intact.
5. Age of onset later than catatonic or disorganized type and the later the onset the better the prognosis.

B. Disorganized (formerly called hebephrenia)
1. Characterized by marked regression to primitive, disinhibited and chaotic behavior.
2. Incoherence, marked loosening of associations, flat or grossly inappropriate affect and pronounced thought disorder.
3. Unkempt appearance, incongruous grinning and grimacing.
4. Early onset usually before age 25.
5. Does not meet criteria for catatonic type.

C. Catatonic
1. Classic feature is a marked disturbance in motor function called waxy flexibility.
2. May involve rigidity, stupor, echopraxia, posturing. Patients may hold awkward positions for long periods of time.
3. Purposeless excitement with risk of injury to self or others may occur.
4. Speech disturbances such as echolalia or mutism may occur.
5. May need medical care for associated malnutrition exhaustion or hyperpyrexia.

D. Undifferentiated type
1. Prominent delusions, hallucinations, incoherence or grossly disturbed behaviour.
2. Does not meet the criteria for paranoid, catatonic or disorganized type.

E. Residual type
1. Absence of prominent delusions, hallucinations, incoherence, or grossly disorganized behaviour.
2. Continuing evidence of the disturbance through two or more residual symptoms (e.g. emotional blunting, social withdrawal).

F. Other subtypes of schizophrenia
1. Positive and Negative symptoms - Another system classifies schizophrenia into one that is based on the presence of positive or negative symptoms. The Positive symptoms include loose associations,
hallucinations, bizarre behavior, and increased speech. The negative symptoms include affective flattening or blunting, poverty of speech or speech content, blocking, poor grooming, lack of motivation, anhedonia, social withdrawal, cognitive defects, and attention deficits. Patients with positive symptoms have a better prognosis than those with negative symptoms.

2. Paraphrenia - Sometimes used as a synonym for paranoid schizophrenia. The term also is used for either a progressively deteriorating course of illness or the presence of a wall-systematized delusional system. These multiple meanings have reduced the usefulness of the term.

3. Simple deteriorative schizophrenia - Characterized by a gradual, insidious loss of drive and ambition. Patients with the disorder are usually not overtly psychotic and do not experience persistent hallucinations or delusions. The primary symptom is the withdrawal of the patient from social and work-related situations.

4. Early-onset schizophrenia - Schizophrenia that develops in childhood. It is very rare.

5. Late-onset schizophrenia - Onset after age 45. More common in women, most often of the paranoid type with good response to medication.

2.7. Course and Prognosis of Schizophrenia (Sadock BJ and Sadock VA, 2010)

A. Course - Prodromal symptoms of anxiety, perplexity, terror, or depression generally precede the onset of schizophrenia, which may be acute or insidious. Prodromal symptoms may be present for months before a definitive diagnosis is made. Onset is generally in the late teens and early 20s, women generally are older at onset than men. Precipitating events (e.g., emotional trauma, use of drugs, a separation) may trigger episodes of illness in predisposed persons. Classically, the course of schizophrenia is one of deterioration overtime, with acute exacerbations superimposed on a chronic picture. Vulnerability to stress is life-long. Postpsychotic depressive episodes may occur in the residual phase. Other comorbidities include substance use disorders, obsessive compulsive disorder, hyponatremia secondary to polydipsia, smoking, and HIV infection.

Relapse rates are approximately 40% in 2 years on medication and 80% in 2 years off medication. Suicide is attempted by 50% of patients, 10% are successful. Violence is a risk. Particularly in untreated patients, risk factors include persecutory delusions, a history of violence, and neurological deficits. The risk for sudden death and medical illness is increased and life expectancy is shortened.

B. Prognosis - In terms of overall prognosis, some investigators have described a loose rule of thirds: approximately one third of patients lead somewhat normal lives, one-third continue to experience significant symptoms but can function within society, and the remaining one-third are markedly impaired and require frequent hospitalization. Approximately 10% of this final third of patients require long-term institutionalization. In general, women have a better prognosis than do men. (Lane C, 2012,
Review of Literature

Bustillo JR, 2008; Stefan et al., 2002 and National Institute of Health for Health and Clinical Excellence 2011; Encyclopedia of Mental Disorders, 2011)

Good Prognostic factors:
- Later age onset or sudden onset
- Female gender
- Fewer negative symptoms
- Good premorbid functioning (Merck)
- Good premorbid occupational and social adjustment
- No family history of schizophrenia
- Family history of mood disorders other than schizophrenia
- Good support system
- Good adherence to prescribed medication
- Paranoid or nondeficit subtype
- Minimal cognitive impairment

Poor Prognostic factors:
- Young age of onset
- Early or insidious onset of psychosis
- Male gender (An atlas of schizophrenia)
- Long duration of untreated psychosis (DUP)
- Depressive symptoms/ Higher number of negative symptoms
- Continued substance abuse
- Family history of schizophrenia
- Poor premorbid functioning
- Poor premorbid adjustment
- Low IQ, low social class, social isolation
- Poor or no support system
- Command auditory hallucinations
- Noncompliance with prescribed treatment
- Poor response to antipsychotic drugs
- Disorganized or deficit subtype

2.8. Schizophrenia Treatment – An Overview (Sadock BJ and Sadock VA, 2010)
Clinical management of the schizophrenic patient may include hospitalization and antipsychotic medication in addition to psychosocial treatments, such as behavioral, family group, individual and social skills and rehabilitation therapies. Any of these treatment modalities can be given on an inpatient or
outpatient basis. Indications for hospitalization include: posing a danger to others, suicidality, severe symptomatology leading to poor self-care or risk for injury secondary to disorganization, diagnostic evaluation, failure to respond to treatment in less restrictive settings, complicating comorbidities and the need to alter complex drug treatment regimens.

A. Pharmacotherapy. The antipsychotic drugs include the first-generation dopamine receptor antagonists and the second-generation agents such as serotonin-dopamine antagonists (SDAs).

1) Choice of antipsychotic drug.

a. First-generation antipsychotics (also known as Typical antipsychotics, or dopamine receptor antagonists) - the classic antipsychotic drugs, which are often effective in the treatment of positive symptoms of schizophrenia. High-potency agents (e.g., haloperidol) are most likely to cause extrapyramidal side effects such as akathisia, acute dystonia, and pseudoparkinsonism. Low-potency agents (e.g., chlorpromazine) are more sedating, hypotensive, and anticholinergic. These agents can cause tardive dyskinesia at a rate of roughly 5% per year of exposure. A significant portion of patients are either unresponsive to or intolerant of these drugs.

b. Second-generation antipsychotics (also known as Atypical, Novel or Serotonin Dopamine Antagonists (SDA)) are the newer-generation antipsychotics drugs that provide potent 5-HT2 receptor blockade and varying degrees of D3-receptor blockade, in addition to other receptor effects. In comparison with the dopamine receptor antagonist (typical agent), these drugs improve two classes of disabilities typical of schizophrenia (1) positive symptoms such as hallucinations, delusions, disordered thought and agitation and (2) negative symptoms such as withdrawal, flat affect, anhedonia, poverty of speech and cognitive impairment. They cause fewer extrapyramidal side effects, usually do not elevate prolactin levels (with the exception of risperidone) and are less likely to cause tardive dyskinesia. Clozapine is the most atypical in that it causes minimal or no extrapyramidal side effects, regardless of dosage, seldom causes tardive dyskinesia, and is extremely effective in treating refractory patients despite weak D2 receptor blockade. As a group, these agents can be highly sedating and cause weight gain in excess of that associated with the dopamine receptor antagonists (with the exception of risperidone). The second-generation drugs are widely prescribed as first-line treatment for patients with schizophrenia. They include aripiprazole, risperidone, olanzapine, paliperidone, clozapine, ziprasidone, and asenapine.

2) Dosage. A moderate fixed dose that is maintained for 4 to 6 weeks (or longer in more chronic cases) is recommended for acute psychotic episodes. High dosages of antipsychotics (>1g of chlorpromazine equivalents) and rapid neuroleptization are no longer recommended, as they increase side effects without enhancing efficacy. Typical therapeutic dosages are 4 to 6 mg of...
risperidone a day, 10 to 20 mg of olanzapine a day and 6 to 20 mg of haloperidol a day. First-episode patients may respond well to lower dosages, whereas selected chronic or refractory patients may rarely require higher dosages. An antipsychotic response develops gradually. Agitation can be managed with benzodiazepines (e.g., 1 to 2 mg of lorazepam three or four times daily) on a standing or as-needed basis while an antipsychotic response is awaited. Patients who are noncompliant because of lack of insight may benefit from long-acting injectable antipsychotics (e.g., 25 mg of fluphenazine decanoate intramuscularly every 2 weeks, 100 to 200 mg of haloperidol decanoate intramuscularly every 4 weeks, Risperidone long-acting 25-50 mg IM every 2 weeks). Patients should first be treated with oral preparations of these drugs to establish efficacy and tolerability.

3) **Maintenance** Schizophrenia is usually a chronic illness, and long-term treatment with antipsychotic medication is usually required to decrease the risk for relapse. If a patient has been stable for approximately 1 year, then the medication can be gradually decreased to the minimum effective dosage possibly at the rate of 10 to 20% per month. During dosage reduction, patients and their families must be educated to recognize and report warning signs of relapse, including insomnia, anxiety, withdrawal, and odd behavior. Strategies for dose reduction must be individualized based on the severity of past episodes, stability of symptoms, and tolerability of medication.

4) **Other drugs**: If standard antipsychotic medication alone is ineffective, several other drugs have been reported to cause varying degrees of improvement. The addition of lithium may be helpful in a significant percentage of patients. Propranolol, benzodiazepines, valproic acid or divalproex and carbamazepine have been reported to lead to improvement in some cases.

**B. Electroconvulsive therapy (ECT)** Can be effective for acute psychosis and catatonic subtype. Patients in whom the illness has lasted less than 1 year are most responsive. ECT is a promising treatment for refractory positive symptoms. It has been shown to have synergistic efficacy with antipsychotic drugs.

**C. Psychosocial interventions.** Antipsychotic medication alone is not as effective in treating schizophrenic patients as are coupled with psychosocial interventions.

1) **Behavior therapy** Desired behaviors are positively reinforced by rewarding them with specific tokens, such as trips or privileges. The intent is to generalize reinforced behavior to the world outside the hospital ward.

2) **Group Therapy** Focus is on support and social skills development (activities of daily living). Groups are especially helpful in decreasing social isolation and increasing reality testing.

3) **Family therapy.** Family therapy techniques can significantly decrease relapse rates for the schizophrenic family member. Multiple family groups, in which family members of schizophrenic patients discuss and share issues, have been particularly helpful.

4) **Supportive Psychotherapy.** Traditional insight-oriented psychotherapy is not usually recommended in treating schizophrenic patients because their egos are too fragile. The rule is that...
as much insight as a patient desires and can tolerate is an acceptable goal. Supportive therapy (which may include advice, reassurance, education, modeling, limit setting, and reality testing) is generally the therapy of choice. A type of supportive therapy called personal therapy involves a heavy reliance on the therapeutic relationship, with instillation of hope and imparting of information.

5) **Social Skills Training** Attempts to improve social skills deficits, such as poor eye contact, lack of relatedness, inaccurate perceptions of others, and social inappropriateness, by means of supportive structurally based and sometimes manually based therapies (often in group settings), which utilize homework, videotapes and role playing.

6) **Case Management** Responsible for the schizophrenic patient's concrete needs and coordination of care. Case managers participate in coordinating treatment planning and communication between various providers. They help patients make appointments, obtain housing and finance benefits, and navigate the health care system, and also provide outreach and crisis management to keep patients in treatment.

7) **Support groups.** Such groups provide support, information, and education for patients and their families.

### 2.9. Antipsychotic Drugs

#### 2.9.1. A Brief Historical Perspective

The history of modern antipsychotic drug development has had a long and torturous course, often based on chance findings that bear little relationship to the intellectual background driving observations. (Shen W W., 1999) Schizophrenia treatments have gone through vast changes in the past century. The reigning theory of madness was based on the antiphlogistic or humoral theory of disease. This theory had been in vogue since the time of Hippocrates (460–377 B.C.) and was elaborated upon by Galen (A.D 129–199). Both mental and physical disorders were considered by Galen to be caused by an excess (plethora) of one of the four humors: black bile, yellow bile, blood, and phlegm. So, the cure was to remove the excess by bleeding the patient or by using purgatives or laxatives. In the early 20th century it was noticed that a higher body temperature reduced the symptoms of schizophrenia. Patients were injected with sulphur in oil to increase their body temperature. Many other therapies such as gas therapy, insulin shock therapy and temple sleep therapy were all tried unsuccessfully (Mathias K, 2011) and dominated until the psychopharmacological revolution in the 1950s (Stanislav Grof, 2011).

The tranquilizers have been in use in some form or other since ancient times. The treatment strategies in ancient India were not limited to the psychological means, they also included an amazing pharmacopeia. Of the many medicinal herbs, two deserve special attention. A plant with psychedelic properties, whose identity
was lost in the course of time, received much attention in the Rigveda and was considered so powerful that it was given the name of a god, Soma. The Ayurvedic plant Rauwolfia serpentina used for treatment of insanity, one of the 500 herbs mentioned in the ancient Charaka Samhita, became the source of reserpine, an important prototype of modern tranquilizers. Rauwolfia is known for its ability to lower blood pressure. Used for many years in India for the treatment of serious mental illness, it was frequently referred to there as the "insanity herb." Most often, its roots were crushed and consumed in a tea. In 1943 an Indian physician named Rustom Jai Vakil (1911–1974) wrote about the plant's success in treating mental illness. It wasn't long before Western doctors began studying Rauwolfia, hoping that it could help patients with severe psychiatric disorders. American doctor Robert Wallace Wilkins (1906–2003) of Boston University Medical School conducted extensive research on Rauwolfia serpentina after hearing about its use in India. In 1954, he showed that reserpine, an indole alkaloid and the active ingredient in Rauwolfia, was successful in treating both hypertension and severe psychiatric disorders such as schizophrenia and other psychoses. Almost immediately the new drug (sold under the brand name Serpasil) became the most popular way to treat such disorders (Nizamie and Goyal, 2010).

In 1891, Paul Ehrlich observed the antimalarial effects of 'methylene blue, a phenothiazine derivative.' Later, the phenothiazines were developed for their antihistaminergic properties (Shen W.W. 1999).

In 1951, Laborit and Huguenard administered the 'aliphatic phenothiazine, chlorpromazine,' to patients for its potential anesthetic effects during surgery. (Shen W.W. 1999)

In 1952, Hamon et al. and Delay et al. extended the use of this treatment in psychiatric patients and serendipitously uncovered its antipsychotic activity (Shen W.W 1999). Pharmacological investigation showed that phenothiazines, the first-generation antipsychotic agents, block many different mediators, including histamine, catecholamines, acetylcholine and 5-HT, and this multiplicity of actions led to the trade name Largactil for chlorpromazine. (Stahl SM, 2008)

Between 1954 and 1975, about 15 antipsychotic drugs were introduced in the United States and about 40 throughout the world.

The discovery of antipsychotics in the 1950s revolutionized the treatment of schizophrenia and focused on the positive symptoms. By the 1960s, however, it became evident that the reduction in positive symptoms did not lead to recovery from schizophrenia and did not significantly improve the functional outcome. The advent of the novel antipsychotics during the last 15 years represents a significant improvement over the effectiveness of conventional antipsychotics (Shahin Akhondzadeh, 2006). Thereafter, there was a hiatus in the development of antipsychotics until the introduction of clozapine treatment in the United States in 1990 opened the era of "atypical" antipsychotic drugs, which show a reduced potential to induce extrapyramidal symptoms (EPS), an increased efficacy for the negative symptoms of schizophrenia, no elevation of prolactin
after chronic use (except risperidone), and, at least for clozapine, effectiveness in some patients previously regarded as treatment-refractory (Shen W.W., 1999). These agents are, however, not a magic bullet and bear their own side effects, such as weight gain, diabetes, hyperprolactinemia, and QTc prolongation. Nevertheless, at this point, they seem to be more effective and safer than the conventional antipsychotics. Moreover, advances in the treatment of schizophrenia have been and continue to be urgently needed. (Shahin A, 2006)

Fig 10. Introduction of Antipsychotics (Ref.: Tandon & Jibson, 2003)

Psychotic illnesses include various disorders, but the term antipsychotic drugs - previously known as neuroleptic drugs, antischizophrenic drugs or major tranquillizers - conventionally refers to those used to treat (psychotic symptoms of) schizophrenia.

The term ‘neuroleptic’ was initially introduced to describe the characteristic emotional quietening, indifference and psychomotor slowing produced by chlorpromazine to contrast the effects of drugs such as sedatives and other CNS depressants (Brunton LL, Chabner BA and Knollmann BC, 2011). These drugs were also called neuroleptics because they caused catalepsy in rodents and extrapyramidal side effects (EPSs) in humans (Meltzer H.Y., 2002). Although the term neuroleptic initially encompassed this whole unique neuroleptic syndrome and is still used as a synonym for antipsychotic, it now is used to emphasize the more neurological aspects of the syndrome (i.e. the parkinsonian and other extrapyramidal effects).

The beneficial effects of antipsychotic drugs are not limited to schizophrenia. They also are employed in disorders ranging from postsurgical delirium and amphetamine intoxication to paranoia, mania, psychotic depression, and the agitation of Alzheimer’s dementia (although their efficacy in this disorder is not proven). They are especially useful in severe depression and possibly in other conditions marked by severe turmoil or agitation (Brunton LL, Chabner BA and Knollmann BC, 2011). Pharmacologically, most are dopamine receptor antagonists, although many of them also act on other targets, particularly 5-hydroxytryptamine (5-HT) receptors, which may contribute to their clinical efficacy. Existing drugs have many drawbacks in terms of their efficacy and side effects. Gradual improvements have been achieved with the newer drugs, but radical new approaches will probably have to wait until there is better understanding of the causes and underlying pathology of the disease, which are still poorly understood.
2.9.2. Classification and Pharmacology of Antipsychotic Drugs

More than 30 different antipsychotic drugs are available for clinical use. These can be broadly divided into two groups - those drugs that were originally developed (e.g., chlorpromazine, haloperidol and many similar compounds), often referred to as first-generation, conventional or typical antipsychotic drugs, and more recently developed agents (e.g., clozapine, risperidone), which are termed 'second-generation' or 'novel' or 'atypical' antipsychotic drugs. (Rang HP et al., 2011)

The term 'atypical' is widely used but not clearly defined. In effect, it refers to the diminished tendency of the newer compounds to cause unwanted motor side effects, but it is also used to describe compounds with a different pharmacological profile from first-generation compounds; several of these newer compounds improve the negative as well as the positive symptoms. In practice, however, it often serves-not very usefully-to distinguish the large group of similar first-generation dopamine antagonists from the more diverse group of newer compounds described below (Rang HP et al., 2011).

In the past, the chemical structure of selected (typical antipsychotic) agents was informative regarding their antipsychotic activity, since most were derived from phenothiazine or butyrophenone structures. Presently however, antipsychotic agents include many different chemical structures with a range of activities at different neurotransmitter receptors (e.g., 5-HT₂A antagonism, 5-HT₁A partial agonism). As a result, structure-function (activity) relationships (SAR) that were relied upon in the past have become less important. Instead, receptor-function relationships and functional assays are more clinically relevant. Aripiprazole represents a good example of how an examination of the structure provides little insight into its mechanism, which is based on dopamine partial agonism.

Detailed knowledge of relative potencies antipsychotics based on receptor affinities (given in table later) and the functional effect at specific receptors (e.g., full, partial or inverse agonism or antagonism) can provide important insight into the therapeutic and adverse effects of antipsychotic agents. Nevertheless, there are limits. For example, it is not known which properties are responsible for clozapine's unique effectiveness in refractory schizophrenia, although many hypotheses exist. Other notable antipsychotic properties not fully explained by receptor parameters include the reduced seizure threshold, the unexpected extent of prolactin elevation for risperidone and paliperidone, the effects of antipsychotic agents on metabolic function, and the increased risk for cerebrovascular events and mortality among dementia patients. (Brunton LL, Chabner BA and Knollmann BC, 2011)
2.9.3. Antipsychotic Agents – Chemical Structures

A. TYPICAL ANTIPSYCHOTICS (Gattaz WF & Busatto G, 2009)

I. PHENOTHIAZINES
(a) Aliphatic side chain (low–medium potency agents): Chlorpromazine, chlorproethazine, cyamemazine, levomepromazine, promazine, triflupromazine.
(b) Piperidine side chain (low–medium potency agents): Thioridazine, mesoridazine, piperacetazine, pipoptiazine, propericiazine, sulfuridazine.
(c) Piperazine side chain (medium–high potency agents): Trifluoperazine, fluphenazine, prochlorperazine, perphenazine, thioproperazine, acetophenazine, butaperazine, dixyazine, perazine, thiopropazate

II. BUTYROPHENONES (high-potency agents): Haloperidol, droperidol, trifluperidol, benperidol, bromperidol, fluanisone, melperone, moperone, pipamperone, timperone.

III. THIOXANTHENES (medium–high potency agents): Thiouixene, chlorprothixene, clopentinox, flupenthixol, zuclopenthixol.

IV. DIHYDROINDOLONES (low–medium potency agents): Molindone, oxypertine

V. DIBENZOEPINES (low–medium potency agents): Loxapine, clozapine.

VI. DIPHENYLBUTYLPIPERIDINES (high-potency agents): Pimozide, fluspirilene, penfluridol

VII. BENZAMIDES (low-potency agents): Sulfiride, nemonapride, sultopride, tiapride

VIII. IMINODIBENZYL (medium-potency agents): Clozapamine, mosapramine.

B. ATYPICAL ANTIPSYCHOTICS

I. BENZO (DIAZE- or THIAZE-) PINES (low and medium–high potency agents): Clozapine, olanzapine, quetiapine

II. INDOLONES and DIONES (low–medium and high-potency agents): Risperidone, paliperidone, iloperidone, ziprasidone, lurasidone, sertindole, arsipiprazole, perospirone.

III. BENZAMIDE (low-potency agents): Amisulpride.


Some New Antipsychotics in the Pipeline: Bifeprunox (Minimal D2 receptor agonism with 5-HT receptor agonism), LY2140023 (Stimulates glutamate receptors), ATI-9242 (Moderate D2 receptor affinity and a high 5HT3/D2 binding ratio), Blonanserin (5-HT2 receptor antagonist and Dopamine receptor D2 antagonist) [EDinformatics.com, 1999 (Online) url www.edinformatics.com/news/drugs_for_schizophrenia.htm (Accessed. 23, October 2012)]
a) Typical Antipsychotics – Molecular Structures:

**Fig 11**

**Phenothiazine derivatives**

- Chlorpromazine
  \[
  \text{CH}_3-\text{CH}_2-\text{CH}_2-N-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}^+\text{Cl}^-
  \]

- Thioridazine
  \[
  \text{CH}_3-N-\text{CH}_2-\text{CH}_2-N-\text{CH}_2-\text{CH}_2-\text{N}^+\text{Cl}^-
  \]

- Aliphatic side chain
  \[
  \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}^+\text{Cl}^-
  \]

- Piperazine side chain
  \[
  \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{N}^+\text{Cl}^-
  \]

- Thiothixene
  \[
  \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{N}^+\text{Cl}^-
  \]

**Thioxanthene derivative**

- Chlorpromazine
  \[
  \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{N}^+\text{Cl}^-
  \]

- Substituting C for N in the nucleus
  \[
  \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{N}^+\text{Cl}^-
  \]

- Haloperidol
  \[
  \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{N}^+\text{Cl}^-
  \]

**Source** Katzung BG, Masters SB, Trevor AJ. Basic & Clinical Pharmacology, 11th Edition

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b) Atypical Antipsychotics – Molecular Structures:  **Fig. 12.** (Ref., Sadock, Sadock & Ruiz, 2009)

**Dibenzodiazepine**

- Olanzapine

- Quetiapine

**Benzosaxazole**

- Risperidone

- Paliperidone

**Arylpyridylindole**

- Aripiprazole

**Benzothiazole**

- Ziprasidone

Source: Katzung BG, Masters SB, Trevor AJ. Basic & Clinical Pharmacology, 11th Edition
2.9.4. Antipsychotics – Pharmacodynamic Aspects

Table 2. Potencies of Antipsychotic Agents at Neurotransmitter Receptors

<table>
<thead>
<tr>
<th>DOPAMINE</th>
<th>SEROTONIN</th>
<th>5-HT2A/D2</th>
<th>Ratio</th>
<th>DOPAMINE</th>
<th>MUSCARINIC</th>
<th>ADRENERGIC</th>
<th>HISTAMINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2</td>
<td>5-HT1A</td>
<td>5-HT2A</td>
<td></td>
<td>D1</td>
<td>D4</td>
<td>M1</td>
<td>α1A</td>
</tr>
<tr>
<td>Typical Agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1.2</td>
<td>2100</td>
<td>57</td>
<td>4500</td>
<td>47</td>
<td>120</td>
<td>5.5</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.8</td>
<td>1000</td>
<td>3.2</td>
<td>990</td>
<td>3.9</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>0.7</td>
<td>410</td>
<td>50</td>
<td>1360</td>
<td>72</td>
<td>51</td>
<td>410</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>0.8</td>
<td>420</td>
<td>5.6</td>
<td>130</td>
<td>7.4</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>Loxapine</td>
<td>11</td>
<td>2550</td>
<td>4.4</td>
<td>13</td>
<td>0.4</td>
<td>54</td>
<td>8.1</td>
</tr>
<tr>
<td>Molindone</td>
<td>0.1</td>
<td>3800</td>
<td>&gt;5000</td>
<td>&gt;10,000</td>
<td>&gt;250</td>
<td>&gt;10,000</td>
<td>&gt;2000</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>8.0</td>
<td>140</td>
<td>28</td>
<td>53</td>
<td>3.5</td>
<td>94</td>
<td>6.4</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>3.6</td>
<td>2120</td>
<td>3.6</td>
<td>16</td>
<td>1</td>
<td>76</td>
<td>12</td>
</tr>
<tr>
<td>Atypical Agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asenapine</td>
<td>1.4</td>
<td>2.7</td>
<td>0.1</td>
<td>0.03</td>
<td>0.05</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>6.8</td>
<td>12.0</td>
<td>0.6</td>
<td>13</td>
<td>0.1</td>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>Sertindole</td>
<td>2.7</td>
<td>280</td>
<td>0.4</td>
<td>0.90</td>
<td>0.2</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Zotepine</td>
<td>8.0</td>
<td>470</td>
<td>2.7</td>
<td>3.2</td>
<td>0.3</td>
<td>71</td>
<td>39</td>
</tr>
<tr>
<td>Risperidone</td>
<td>3.2</td>
<td>420</td>
<td>0.2</td>
<td>50</td>
<td>0.05</td>
<td>240</td>
<td>7.3</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>4.2</td>
<td>20.0</td>
<td>0.7</td>
<td>48</td>
<td>0.2</td>
<td>41</td>
<td>54</td>
</tr>
<tr>
<td>Illoperidone</td>
<td>6.3</td>
<td>90</td>
<td>5.6</td>
<td>43</td>
<td>0.9</td>
<td>130</td>
<td>25</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>1.6</td>
<td>6.0</td>
<td>8.7</td>
<td>22</td>
<td>5.0</td>
<td>1200</td>
<td>510</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>6.4</td>
<td>10,000</td>
<td>&gt;10,000</td>
<td>&gt;10,000</td>
<td>&gt;1000</td>
<td>&gt;10,000</td>
<td>&gt;54</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>31</td>
<td>2300</td>
<td>3.7</td>
<td>10</td>
<td>0.1</td>
<td>70</td>
<td>18</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>380</td>
<td>390</td>
<td>640</td>
<td>1840</td>
<td>2.0</td>
<td>990</td>
<td>2020</td>
</tr>
<tr>
<td>Clozapine</td>
<td>160</td>
<td>120</td>
<td>5.4</td>
<td>9.4</td>
<td>0.03</td>
<td>270</td>
<td>24</td>
</tr>
</tbody>
</table>

Data are averaged K values (nM) from published sources determined by competition with radioligands for binding to the indicated cloned human receptors. Data derived from receptor binding to human or rat brain tissue is used when cloned human receptor data is lacking. (Brunton LL, Chabner BA and Knollmann BC, 2011)

Fig.13. Antipsychotics - Correlation between the Clinical Potency and the Affinity for Dopamine-2 Receptors (Ref.: Rang HP et al., 2011)

IC50 (mol/l)
2.9.5. Antipsychotics – Site and Mechanism of Action

Most antipsychotics block dopamine D2 receptors in the mesolimbic pathway to the nucleus accumbens and this alleviates the positive symptoms of schizophrenia. Whereas atypical or serotonin-dopamine antagonist (SDA) antipsychotics (e.g., clozapine, olanzapine, risperidone) block serotonin 5-HT2 receptors in the mesocortical pathway to prefrontal lobe cortex. This increases the release of dopamine (DA) and thereby alleviates the negative symptoms of schizophrenia.

<table>
<thead>
<tr>
<th>Dopamine Tract</th>
<th>Origin</th>
<th>Innervation</th>
<th>Function</th>
<th>Dopamine Antagonist Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesolimbic</td>
<td>Midbrain ventral tegmentum (A10 area)</td>
<td>Limbic areas (e.g., amygdala, olfactory tubercle, septal nuclei), cingulate gyrus</td>
<td>Arousal, memory, stimulus processing, motivational behavior</td>
<td>Relief of psychosis</td>
</tr>
<tr>
<td>Mesocortical</td>
<td>Midbrain ventral tegmentum (A10 area)</td>
<td>Frontal and prefrontal lobe cortex</td>
<td>Cognition, communication, social function, response to stress</td>
<td>Relief of psychosis, Akathisia</td>
</tr>
<tr>
<td>Nigrostriatal</td>
<td>Substantia nigra (A9 area)</td>
<td>Caudate nucleus, Putamen</td>
<td>Extrapyramidal system, movement</td>
<td>Movement disorders</td>
</tr>
<tr>
<td>Tuberoinfundibular</td>
<td>Hypothalamus</td>
<td>Pituitary gland</td>
<td>Regulates prolactin release</td>
<td>Increased prolactin concentrations</td>
</tr>
</tbody>
</table>

Table 3. Brain Dopaminergic Tracts and Effects of Dopamine Antagonists substantiating Dopamine Hypothesis in Schizophrenia

(DePiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, L Posey M, 2011)

2.9.6. Mechanism of action of antipsychotic drugs (Rang HP et al., 2011)

- Antipsychotic drugs are antagonists or partial agonists at D2 dopamine receptors, but most also block a variety of other receptors.
- Imaging studies suggest that antipsychotic therapeutic effect requires about 80% occupancy of D2 receptors.
- Antipsychotic potency generally runs parallel to activity on D2 receptors.
- Activities at receptors such as 5-HT2A and muscarinic may reduce their extrapyramidal side effects.
- Activity at muscarinic, H1 and α receptors may determine unwanted side effect profile.

The typical antipsychotic agents block D2 receptors stereoselectively for the most part, and their binding affinity is very strongly correlated with clinical antipsychotic and extrapyramidal potency. In vivo imaging studies of D2-receptor occupancy indicate that for antipsychotic efficacy, the typical antipsychotic drugs must be given in sufficient doses to achieve 60% occupancy of striatal D2 receptors. This is not required for the atypical antipsychotic drugs such as clozapine and olanzapine, which are effective at lower occupancy levels of 30–50%, most likely because of their concurrent high occupancy of 5-HT2A receptors. The typical antipsychotic drugs produce EPS when the occupancy of striatal D2 receptors reaches 80% or higher. (Katzung BG, Masters SB & Trevor AJ, 2012)
### 2.9.7. Antipsychotics - Receptor Pharmacology

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Therapeutic Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blockade of D₂-dopaminergic</td>
<td>Alleviation of positive symptoms of schizophrenia</td>
<td>Extrapyramidal effects (e.g., akathisia, dystonia, dyskinesia, parkinsonism), elevated prolactin</td>
</tr>
<tr>
<td>receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blockade of D₄-dopaminergic</td>
<td>Alleviation of negative symptoms of schizophrenia and decrease in the incidence of extrapyramidal side effects</td>
<td></td>
</tr>
<tr>
<td>receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blockade of 5-HT₂-dopaminergic</td>
<td>Alleviation of negative symptoms of schizophrenia and decrease in the incidence of extrapyramidal side effects</td>
<td>Anxiety, insomnia, increase in appetite and weight</td>
</tr>
<tr>
<td>receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blockade of α₁-adrenergic</td>
<td>----</td>
<td>Dizziness, orthostatic hypotension, reflex tachycardia</td>
</tr>
<tr>
<td>receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blockade of H₁-Histaminergic</td>
<td>----</td>
<td>Drowsiness, increase in appetite and weight</td>
</tr>
<tr>
<td>receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blockade of muscarinic receptors</td>
<td>----</td>
<td>Blurred vision, dry mouth, constipation, urinary retention, memory dysfunction</td>
</tr>
</tbody>
</table>

[Adapted from Tandon & Jibson (2003), Mathews & Muzina (2007)]

### a) At Dopamine Receptors

While emerging data indicate that stimulation of glutamate or muscarinic receptors may confer antipsychotic properties, no clinically available effective antipsychotic is devoid of D₂ antagonistic activity. This reduction in dopaminergic neurotransmission is presently achieved through one of two mechanisms. D₂ antagonism or partial D₂ agonism, of which aripiprazole is the only current example (Another partial agonist, bifeprunox has yet failed to gain FDA approval.) (Brunton LL, Chabner BA and Knollmann BC, 2011)

It is the antagonism of D₂ receptors in the mesolimbic pathway that is believed to relieve the positive symptoms of schizophrenia. Unfortunately, systemically administered antipsychotic drugs do not discriminate between D₂ receptors in distinct brain regions and D₂ receptors in other brain pathways will also be blocked. Thus, antipsychotic drugs produce unwanted motor effects (block of D₂ receptors in the nigrostriatal pathway), enhance prolactin secretion (block of D₂ receptors in the tubero-infundibular pathway), reduce pleasure (block of D₂ receptors in the reward component of the mesolimbic pathway) and perhaps even worsen the negative symptoms of schizophrenia (block of D₂ receptors in the prefrontal cortex, although these are only expressed at a low density-D₂ receptors being in greater abundance). While all antipsychotic drugs block D₂ receptors and should therefore in theory induce all of these unwanted effects, some have additional pharmacological activity (e.g., mACh receptor antagonism and 5-HT₁A receptor antagonism) that, to varying degrees, ameliorate unwanted effects. 5-HT₁A antagonism may help to alleviate the negative and cognitive impairments of schizophrenia (Brunton LL, Chabner BA and Knollmann BC, 2011)
Antipsychotic drugs have classically been thought to have a delayed onset to their therapeutic actions, even though their dopamine receptor-blocking action is immediate. This view has, however, been called into question (Kapur et al., 2005; Leucht et al., 2005). In animal studies, chronic antipsychotic drug administration does produce compensatory changes in the brain, for example a reduction in the activity of dopaminergic neurons and proliferation of dopamine receptors, detectable as an increase in haloperidol binding (Seeman, 1987), with a pharmacological supersensitivity to dopamine reminiscent of the phenomenon of denervation supersensitivity. The mechanism(s) of these delayed effects are poorly understood. They are likely to contribute to the development of unwanted tardive dyskinesias (see below). The sedating effect of antipsychotic drugs occurs extremely rapidly, allowing them to be used in acute behavioural emergencies. (cited by Rang HP et al, 2011)

Levels of central D₂ occupancy estimated by positron emission tomography (PET) brain imaging in patients treated with antipsychotic drugs support conclusions arising from laboratory studies that receptor occupancy predicts clinical efficacy, EPS, and serum level-clinical response relationships. Occupation of >78% of D₂ receptors in the basal ganglia is associated with a risk of EPS across all dopamine antagonist antipsychotic agents, while occupancies in the range of 60-75% are associated with antipsychotic efficacy (Kapur et al., 2000b). With the exception of aripiprazole, all atypical antipsychotic drugs at low doses have much greater occupancy of 5-HT₂A receptors (e.g., 75-99%) than typical agents. (Brunton LL, Chabner BA and & Knollmann BC, 2011)

Functional Interactions between Serotonin-Dopamine System and Their Role in Reducing Extrapyramidal Symptoms (Fig 15. Ref.: Ishigooka J., 2004)

Among atypical agents, clozapine has the highest ratio of 5-HT₂A/D₂ binding. Clozapine’s D₂ occupancy 12-hours post-dose ranges from 51-63% (Kapur et al., 1999), providing evidence for its limited EPS risk. The trough D₂ occupancy for quetiapine is even lower (< 30%), but PET studies obtained 2-3 hours after dosing reveal D₂ receptor occupancies in the expected therapeutic range.
(54-64%), albeit transiently. Ziprasidone absorption is sensitive to the presence of food, but PET studies demonstrate that clinical efficacy occurs when D₂ occupancy exceeds 60%, which corresponds to a minimum daily dose of 120 mg (with food) (Mamo et al., 2004).

b) At Serotonin (5-Hydroxytryptamine) Receptors

Drugs with 5-HT₂₅ antagonism properties (e.g. olanzapine and risperidone) enhance dopamine release in the striatum by reducing the inhibitory effect of 5-HT. This will reduce extrapyramidal side effects (see below). (Rang HP et al., 2011) In contrast, in the mesolimbic pathway, the combined effects of D₂ and 5-HT₂₅ antagonism are thought to counteract the increased dopamine function that gives rise to positive symptoms of schizophrenia. Further, enhancing both dopamine and glutamate release in the mesocortical circuit, 5-HT₂₅ receptor antagonism may improve the negative symptoms of schizophrenia (Stahl, 2008). 5-HT₁₅ receptors are somatodendritic autoreceptors that inhibit 5-HT release. Antipsychotic drugs that are agonists or partial agonists at 5-HT₁₅ receptors (e.g. quetiapine) may work by decreasing 5-HT release thus enhancing dopamine release in the striatum and prefrontal cortex. (Rang HP et al., 2011)

Fig. 16: Receptor Binding Profiles of the Atypical Antipsychotics: (Ref.: Stahl S.M., 2008)

Abbreviations: α, = α₁-adrenergic, α₂ = α₂-adrenergic, D = dopamine, 5HT = serotonin, H = histamine, M = muscarinic, NRI = norepinephrine reuptake inhibitor, SRI = serotonin reuptake inhibitor.
The neuropharmacology and behavioral pharmacology of 5-HT₂ antagonism provide insights into the advantageous properties of medications with these effects (Marek et al., 2003). Antipsychotic agents with appreciable 5-HT₂ affinity have significant effects at both 5-HT₂a and 5-HT₂c receptors with individual medications varying in their relative potencies at each subtype (Tarazi et al., 2002) As discussed previously, atypical antipsychotic agents exhibit potent functional antagonism at both subtypes of 5-HT₂ receptors, but in vitro assays suggest that these effects result from inverse agonism at these G-coupled receptors (Brunton LL, Chabner BA and & Knollmann BC, 2011)

Some antipsychotics are 5-HT₂a agonists/partial agonists (Stahl SM, 2011)
- Clozapine, Ziprasidone, Aripiprazole, Norquetiapine, Asenapine, Lurasidone

Some antipsychotics are 5-HT₂c antagonists
- Clozapine, Olanzapine, Risperidone/paliperidone, Ziprasidone, Norquetiapine, Asenapine

Some antipsychotics are 5-HT₇ antagonists
- Aripiprazole, Amisulpride, Asenapine, Lurasidone

c) At Muscarinic Acetylcholine Receptors
Some phenothiazine antipsychotic drugs (e.g. thioridazine) induce fewer extrapyramidal side effects than others, and this correlates with their affinity as muscarinic antagonists. Also, some newer, atypical drugs possess muscarinic antagonist properties (e.g. olanzapine). In the striatum, dopaminergic nerve terminals are thought to innervate cholinergic interneurons that express inhibitory D₂ receptors. It is suggested that there is normally a balance between D₂ receptor activation and muscarinic receptor activation. Blocking D₂ receptors in the striatum with an antipsychotic agent will result in enhanced acetylcholine release on to muscarinic receptors, thus producing extrapyramidal side effects, which are counteracted if the D₂ antagonist also has muscarinic antagonist activity. Maintaining the dopamine/acetylcholine balance was also the rationale for the use of benztpine (trihexyphenidyl) to reduce extrapyramidal effects of antipsychotic drugs. Muscarinic antagonist activity does, however induce side effects such as constipation, dry mouth and blurred vision (Rang HP et al., 2011)

d) At Alpha Adrenergic Receptors
α₁ Adrenergic antagonism is associated with risk of orthostatic hypotension and can be particularly problematic for elderly patients who have poor vasomotor tone. Compared to high-potency typical agents, low-potency typical agents have significantly greater affinities for α₁ receptors and greater risk for orthostasis. While risperidone has a Kᵢ that indicates greater α₁-adrenergic affinity than chlorpromazine, thioridazine, clozapine, and quetiapine, in clinical practice risperidone is used at 0.01-0.005 times the dosages of these medications, and thus causes a relatively lower incidence of orthostasis in non-elderly patients. Since clozapine-treated patients have few other antipsychotic options, the potent mineralocorticoid fludrocortisone is sometimes tried at the dose of 0.1 mg/day as a volume expander. (Brunton LL, Chabner BA and & Knollmann BC, 2011)
2.9.8. What Makes Atypical Antipsychotics Atypical? (Features differentiating them from Typical) (Fig. 17)

Both FGA and SGA classes exhibit substantial heterogeneity across a range of clinical and pharmacological attributes and no single property can consistently distinguish the existing antipsychotic agents into these two subgroups. In addition to the above anomalies, the dichotomy of first-generation versus secondary generation antipsychotics results in some obvious misclassifications (Noll R, 2009).

Indirect comparisons of efficacy across studies and direct comparisons in the relatively few randomized, controlled head-to-head studies between other SGAs suggest that they are essentially similar with regard to overall efficacy and efficacy in treating positive and negative symptoms; if differences exist, these are small (Tandon et al., 2008). The occasional observation of the superior efficacy of some SGAs over others (Leucht et al. 2009) may be explained by the fact that optimal dose ranges for olanzapine, risperidone, and amisulpride are somewhat better defined than those for quetiapine, ziprasidone, and aripiprazole and other methodological differences (Tandon et al., 2008).

The concept of atypicality was initially based on clozapine’s absence of EPS within the therapeutic range, combined with a prominent role of 5-HT2 receptor antagonism. The hypothesis that a relatively high affinity for the 5-HT2A receptor compared to an affinity for the D2 receptor was the basis for the difference between atypical and typical antipsychotic agents contributed to the development of the newer antipsychotic agents (Meltzer HY, 2002). As subsequent agents were synthesized using clozapine’s 5-HT2/D2 ratio as a model, most of which possessed greater D2 affinity and EPS risk than clozapine, there has been considerable debate on the definition of an atypical antipsychotic agent and its necessary properties (Brunton LL, Chabner BA and Knollmann BC, 2011).

2.9.9. The following pharmacologic and clinical criteria can attribute the agent with atypicality:

(1) atypical antipsychotics have Serotonin 5-HT2A receptors and Dopamine D2 receptors antagonism (SDA) pharmacological properties, whereas conventional antipsychotics are only dopamine D2 receptors antagonists;

(2) atypical antipsychotics improve positive symptoms as well as do conventional antipsychotics as well has extended effect on negative symptoms.

(3) atypical antipsychotics cause fewer EPS than typical antipsychotics;
(4) unlike typical antipsychotics, atypical antipsychotics does not cause prolactin release and consequent endocrine side effects.

Of course, there are exceptions and limitations to the concept of atypicality, which will been seen later.

2.9.10. Difference in Receptor Binding Affinity at Postsynaptic D₂ Receptors (Fig. 18, Ref.: Stahl, SM, 2008)

Because of the biochemical properties (rough binding site) of conventional or typical antipsychotics, their binding to postsynaptic D₂ dopamine receptors is tight and long-lasting. Because of the biochemical properties (smooth binding site) of atypical antipsychotics, their binding to postsynaptic D₂ dopamine receptors is loose and shorter-lasting due to rapid dissociation from the binding site (Stahl S.M., 2008).

Rapid dissociation from D₂ receptors (‘fast OFF’) is one explanation for the improved EPS profile of atypical antipsychotics, and one that is also consistent with the theory of a lower affinity for D₂ receptors for these drugs (Kapur and Seeman 2001, Horacek et al 2006).

2.9.11. Serotonin-Dopamine Antagonism

Clozapine is considered to be the prototype of the atypical antipsychotics. Antipsychotics, as it was the first to be recognized as having few if any extrapyramidal side effects, not causing tardive dyskinesia, and not elevating prolactin.

The hypothesis that a relatively high affinity for the 5-HT₂A receptor compared to an affinity for the D₂ receptor was the basis for the difference between atypical and typical antipsychotic agents contributed to the development of the newer antipsychotic agents (Meltzer H. Y, 2002). As subsequent agents were synthesized using clozapine’s 5-HT₂/D₂ ratio as a model, most of which possessed greater D₂ affinity and EPS risk than clozapine, there has been considerable debate on the definition of an atypical antipsychotic agent and its necessary properties (Brunton LL, Chabner BA and Knollmann BC, 2011). From a pharmacological
perspective, the atypical antipsychotics as a class may be defined in part as serotonin-dopamine antagonists (SDAs) (Stahl S M., 2008).

Serotonin has important influences on dopamine, but that influence is quite different in each of the four brain dopamine pathways. That is, serotonin inhibits dopamine release from dopaminergic axon terminals in the various dopamine pathways, but the degree of control differs from one dopamine pathway to another. Understanding the differential serotonergic control of dopamine release in each of these four pathways is critical to understanding the differential actions of antipsychotic drugs that block only D_2 receptors (i.e., the conventional antipsychotics) versus antipsychotic drugs that block both 5-HT_2A and D_2 receptors (i.e., the atypical antipsychotics) (Stahl S.M., 2008).

a) In case of brain’s mesolimbic dopaminergic pathway –
Both typical and atypical block the D_2 receptors alleviating the positive symptoms of schizophrenia. Dopamine blockade conventional (typical) antipsychotics here results in antipsychotic actions for positive symptoms, but at a cost of worsened, or at least not improved, negative symptoms, production of EPS, tardive dyskinesia, and hyperprolactinemia. On the other hand, in case of atypical antipsychotic (SDA), which also blocks D_2 receptors, the antagonism by serotonin of the effects of dopamine is not robust enough to cause the reversal of D_2 receptors by atypical antipsychotics or to mitigate the actions of atypical antipsychotics on positive symptoms of psychosis. (Stahl S.M., 2008)

b) In case of brain’s mesocortical dopaminergic pathway –
Positron emission tomography scans reveal that an antipsychotic dose of a conventional (typical) antipsychotic drug does not block serotonin 2A receptors in the cortex as expected, because these drugs lack such binding properties, but that an antipsychotic dose of an atypical antipsychotic causes a nearly complete blockade of the serotonin 2A receptors there. Where serotonin 2A receptors are blocked, dopamine is being released, which explains in part why atypical antipsychotics improve negative symptoms better than do conventional antipsychotics. (Stahl S.M., 2008)

In the mesocortical dopamine pathway, atypical antipsychotics with SDA properties have a more profound effect in blocking densely populated cortical serotonin 2A receptors, thereby increasing DA release, than in blocking thinly populated cortical D_2 receptors.

Further, enhancing both dopamine and glutamate release in the mesocortical circuit, 5-HT_2A receptor antagonism by atypical antipsychotics may improve the negative symptoms of schizophrenia. So, when an atypical antipsychotic is administered, negative symptoms are consequently improved, not worsened as they often are with conventional antipsychotics.
c) In case of brain’s nigrostriatal dopaminergic pathway –
In case of typical antipsychotics, the D₂ receptors blockade leads to extrapyramidal side effects (EPS). In case of atypical antipsychotics, ability of serotonin 2A antagonism to play a sort of indirect “tug-of-war” with dopamine 2 antagonism by causing dopamine release, which in turn mitigates or reverses dopamine 2 antagonism. In the nigrostriatal dopamine pathway, positron emission tomography (PET) scans document that atypical antipsychotics bind to fewer D₂ receptors in the basal ganglia in schizophrenic patients than do conventional antipsychotics at matched antipsychotic efficacies. Thus, about 90% of D₂ receptors are blocked when a patient takes an antipsychotic dose of a conventional antipsychotic, but less than 70 to 80% are blocked with an atypical antipsychotic. This puts the threshold of D₂ blockade below the level necessary to produce EPS in many patients (Stahl S. M., 2008).

d) In case of brain’s tuberoinfundibular dopaminergic pathway –
There is an antagonistic and reciprocal relationship between serotonin and dopamine in the control of prolactin secretion from the pituitary lactotroph cells. Thus, when D₂ receptors are blocked by a conventional antipsychotic, dopamine can no longer inhibit prolactin release, so prolactin levels rise. However, in the case of an atypical antipsychotic, there is simultaneous inhibition of 5HT₂A receptors, so serotonin can no longer stimulate prolactin release. This tends to mitigate the hyperprolactinemia of D₂ receptor blockade. Although this is interesting theoretical pharmacology, in practice not all serotonin-dopamine antagonists reduce prolactin secretion to the same extent, and some do not reduce it at all. (Stahl S. M., 2008)

2.9.12. Beyond Serotonin-Dopamine Antagonism
Atypical antipsychotics are not merely simple serotonin-dopamine antagonists (SDAs). In truth, they have some of the most complex mixtures of pharmacologic properties in psychopharmacology. Beyond antagonism of serotonin 2A and dopamine 2 receptors, some agents in this class interact with multiple other receptor subtypes for both dopamine and serotonin, including 5HT₁A, 5HT₁D, 5HT₂C, 5HT₅, 5HT₇, and D₁, D₃, and D₄. Other neurotransmitter systems are involved as well, including both norepinephrine and serotonin reuptake blockade, as well as antimuscarinic, antihistaminic, and alpha 1 adrenergic plus alpha 2 adrenergic blockade. No two atypical antipsychotics, however, have identical binding properties, which probably helps to explain why they all have distinctive clinical properties. (Stahl S. M., 2008)

2.9.13. Exceptions and Limitations to the Concept of Atypicality
Clozapine seemed atypical in that it did not cause extrapyramidal side effects (EPS) in patients or catalepsy in animals, in contrast to the prevailing antipsychotics (haloperidol and chlorpromazine). Through the 1970s and 1980s, “atypical” was synonymous with clozapine. However, with its clinical introduction, additional unique features were highlighted. Specifically, clozapine was found to (a) be effective in at least some
patients for whom the typical neuroleptics had failed, (b) show preferential effects on the so-called negative symptoms (apathy, amotivation, etc), and (c) demonstrate possible benefits on symptoms related to mood and cognition. Although experts can barely agree on a formal definition of atypicality, there is nearly unanimous agreement that all the newly introduced antipsychotic drugs are atypical (Kapur & Ramington, 2001). Clozapine is more effective than other antipsychotic agents in treatment-refractory schizophrenia patients (specifically antipsychotic-refractory positive symptoms), ameliorating symptoms in about one-third of such patients. Reduced EPS liability does not explain this greater efficacy of clozapine.

Loxapine is a serotonin-dopamine antagonist but considered to be a conventional antipsychotic, especially at high doses. Risperidone a serotonin-dopamine antagonist at high doses begin to lose their atypical properties (Stahl SM, 2008).

Aripiprazole in particular is problematic agent for the model based on ratios of 5-HT$_2$ to D$_2$, since its action as partial agonist necessitates very high D$_2$ affinity. Loxapine is another problematic agent for the model since its receptor pharmacology suggests atypical properties based on 5-HT$_2$/D$_2$ ratio; however, in clinical practice its use was associated with the expected higher level of EPS characteristic of typical antipsychotic drugs, perhaps related to the additive D$_2$ antagonist properties of the active metabolite amoxapine These dilemmas have lead some to suggest abandonment or modification of the atypical/typical antipsychotic terminology, perhaps in lieu of the designation by generation (e.g., first, second, etc.), as is used with antibiotics, or some other organizing scheme (Grunder et al., 2009) Nonetheless, the term “atypical” persists in common usage and designates lesser (but not absent) EPS risk and other decreased effects of excessive D$_2$ antagonism, or more accurately, reduction in D$_2$-mediated neurotransmission (Brunton LL, Chabner BA and & Knollmann BC, 2011).


Recent findings reinforce the importance of achieving an antipsychotic effect without EPS. The inconsistently observed greater spectrum of efficacy of SGAs over FGAs is substantially explained by their generally reduced propensity to cause EPS, and when EPS differences between these antipsychotic agents are eliminated, efficacy spectrum differences disappear as well. Thus using any antipsychotic agent as an “atypical” (a robust antipsychotic effect without EPS and without using an anticholinergic agent) is of importance — this leads to modestly greater effects on negative, cognitive, and depressive symptoms.

Thus the “atypical effect” is associated with a perceived broader spectrum of efficacy (advantages with reference to negative, cognitive, and mood symptoms) and a lower risk of tardive dyskinesia Disagreement about the basic definition of atypicality and efforts to define its pharmacological basis led to the replacement
of "atypical antipsychotic" by the term "second-generation antipsychotic." While the dichotomous classification of existing antipsychotic agents into these two subgroups is not valid or useful, the property of atypicality is still relevant. Efforts to elucidate its pharmacological substrate is still of great importance. The term second-generation antipsychotic should be abandoned as it is both uninformative and misleading. The concept of atypicality (the ability to obtain a robust antipsychotic effect without EPS) as originally conceived is still meaningful.

2.10. Animal Screening Tests of Antipsychotics (Katzung BG, Masters SB & Trevor AJ, 2012)
Antipsychotic drugs reduce spontaneous motor activity and in larger doses cause catalepsy, a state in which the animal remains immobile even when placed in an unnatural position. Inhibition of the hyperactivity induced by amphetamine parallels antipsychotic actions of these drugs, whereas their tendency to induce catalepsy parallels extrapyramidal symptoms (Rang HP et al., 2011). Inhibition of conditioned (but not unconditioned) avoidance behavior is one of the most predictive tests of antipsychotic action. Another is the inhibition of amphetamine- or apomorphine-induced stereotyped behavior. Other tests that may predict antipsychotic action are reduction of exploratory behavior without undue sedation, induction of a cataleptic state, inhibition of intracranial self-stimulation of reward areas, and prevention of apomorphine-induced vomiting. Most of these tests are difficult to relate to any model of clinical psychosis.

The psychosis produced by phencyclidine (PCP) has been used as a model for schizophrenia. Because this drug is an antagonist of the NMDA glutamate receptor, attempts have been made to develop antipsychotic drugs that work as NMDA agonists. Sigma receptor and cholecystokinin type b (CCK_b) antagonism have also been suggested as potential targets. Thus far, NMDA receptor-based models have pointed to agents that modulate glutamate release as potential antipsychotics. 5-HT_2A inverse agonists such as pimavanserin, ritanserin, and M100907 are potent inhibitors of PCP-induced locomotor activity, whereas D_2 antagonists are relatively weak in comparison. Thus, atypical antipsychotic drugs that act as 5-HT_2A antagonists appear much more potent than typical antipsychotic drugs in PCP models.

2.11. Pharmacological Effects of Antipsychotics

a) Behavioral Effects
All first-generation antipsychotic drugs inhibit amphetamine-induced behavioural changes, reflecting their action on D_2 receptors. Some atypical drugs have less activity on D_2 receptors and are less active in such models, and also in the catalepsy model. They are, however, as efficacious as the older drugs in pre-pulse inhibition and conditioned avoidance tests. Both classic and atypical drugs, moreover, reduce the hyperactivity caused by phencyclidine (a glutamate antagonist) in rodents. In humans, phencyclidine causes a schizophrenia-like syndrome. Conditioned avoidance and phencyclidine tests in animals may therefore be more appropriate guides to antipsychotic activity in humans (Rang HP et al., 2011).
In humans, antipsychotic drugs produce a state of apathy and reduced initiative. The recipient displays few emotions, is slow to respond to external stimuli and tends to drowse off. The subject is, however, easily aroused and can respond to questions accurately, with no marked loss of intellectual function. Aggressive tendencies are strongly inhibited. Effects differ from those of sedative anxiolytic drugs, which also cause drowsiness and confusion but with euphoria rather than apathy. (Rang HP et al., 2011)

Many antipsychotic drugs are antiemetic, reflecting antagonism at dopamine, muscarinic, histamine and possibly 5-HT receptors. (Rang HP et al., 2011)

b) Electroencephalographic Effects
Antipsychotic drugs produce shifts in the pattern of electroencephalographic (EEG) frequencies, usually slowing them and increasing their synchronization. The slowing (hypersynchrony) is sometimes focal or unilateral, which may lead to erroneous diagnostic interpretations. Both the frequency and the amplitude changes induced by psychotropic drugs are readily apparent and can be quantitated by sophisticated electrophysiologic techniques. Some of the neuroleptic agents lower the seizure threshold and induce EEG patterns typical of seizure disorders; however, with careful dosage titration, most can be used safely in epileptic patients. (Katzung BG, Masters SB & Trevor AJ, 2012)

c) Cardiovascular Effects
The low-potency phenothiazines frequently cause orthostatic hypotension and tachycardia. Mean arterial pressure, peripheral resistance, and stroke volume are decreased. These effects are predictable from the autonomic actions of these agents. Abnormal ECGs have been recorded, especially with thioridazine. Changes include prolongation of QT interval and abnormal configurations of the ST segment and T waves. These changes are readily reversed by withdrawing the drug. Thioridazine, however, is not associated with increased risk of torsade more than other typical antipsychotics, whereas haloperidol, which does not increase QTc, is associated with risk of torsade. (Katzung BG, Masters SB & Trevor AJ, 2012)

Among the newest atypical antipsychotics, prolongation of the QT or QTc interval has received much attention. Because this was believed to indicate an increased risk of dangerous arrhythmias, sertindole has been delayed and ziprasidone and quetiapine are accompanied by warnings. There is, however, no evidence that this has actually translated into increased incidence of arrhythmias. (Katzung BG, Masters SB & Trevor AJ, 2012)

d) Endocrine Effects
Older typical antipsychotic drugs, as well as risperidone and paliperidone, produce adverse effects marked by elevations of prolactin. Newer antipsychotics such as olanzapine, quetiapine, and aripiprazole cause no or
minimal increases of prolactin and reduced risks of extrapyramidal system dysfunction and tardive dyskinesia, reflecting their diminished D$_2$ antagonism. (Katzung BG, Masters SB & Trevor AJ, 2012)

Weight gain is frequently reported in both adults and children receiving antipsychotics. Schizophrenic patients have a higher prevalence of type II diabetes than the nonschizophrenic population. Beyond this, antipsychotics may adversely affect glucose levels in diabetic patients. Data collected from the FDA MedWatch Drug Surveillance System for clozapine, olanzapine, quetiapine, and risperidone indicate that nearly 60% of the new-onset diabetes reported occurred within the first 6 months of treatment initiation. Treatment with at least some SGAs and phenothiazines appears associated with elevations in serum triglycerides and cholesterol. (DiPiro JT and others, 2011) See Unwanted Effects, below.

2.12. Pharmacokinetics of Antipsychotics

Chlorpromazine, in common with other phenothiazines, is erratically absorbed after oral administration. The given figure (fig. 19) shows the wide range of variation of the peak plasma concentration as a function of dosage in 14 patients. Among four patients treated at the high dosage level of 6-8 mg/kg, the variation in peak plasma concentration was nearly 90-fold; two showed marked side effects, one was well controlled and one showed no clinical response. (Rang HP et al., 2011)

The relationship between the plasma concentration and the clinical effect of antipsychotic drugs is highly variable, and the dosage has to be adjusted on a trial-and-error basis. This is made even more difficult by the fact that at least 40% of schizophrenic patients fail to take drugs as prescribed. It is remarkably fortunate that the acute toxicity of antipsychotic drugs is slight, given the unpredictability of the clinical response. The plasma half-life of most antipsychotic drugs is 15-30 h, clearance depending entirely on hepatic transformation by a combination of oxidative and conjugative reactions.

Most antipsychotic drugs can be given orally or in urgent situations by intramuscular injection. Slow-release (depot) preparations of many are available, in which the active drug is esterified with heptanoic or decanoic acid and dissolved in oil. Given as an intramuscular injection, the drug acts for 2-4 weeks, but initially may produce acute side effects. These preparations are widely used to minimise compliance problems (Rang HP et al., 2011). With the exception of amisulpride, currently available atypical antipsychotics are extensively metabolized, primarily by oxidative processes, but also by direct glucuronidation.
### Table 5. Main Pharmacokinetic Parameters of Some Atypical Antipsychotics (Ref Spina E and Leon JD, 2007)

<table>
<thead>
<tr>
<th></th>
<th>Bioavailability (%)</th>
<th>Protein binding (%)</th>
<th>Half-life (hours)</th>
<th>Time to reach steady-state (days)</th>
<th>Enzymes responsible for biotransformation</th>
<th>Active metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>12-81</td>
<td>&gt;90</td>
<td>6-33</td>
<td>4-8</td>
<td>CYP1A2, CYP2C19, (CYP3A4, CYP2D6)</td>
<td>Norclozapine</td>
</tr>
<tr>
<td>Risperidone</td>
<td>68</td>
<td>90</td>
<td>3-24</td>
<td>4-6</td>
<td>CYP2D6, CYP3A4</td>
<td>9-Hydroxy-risperidone</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>60-80</td>
<td>93</td>
<td>20-70</td>
<td>5-7</td>
<td>CYP1A2, CYP2D6</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Not available</td>
<td>83</td>
<td>5-8</td>
<td>2-3</td>
<td>CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Sertindole</td>
<td>75</td>
<td>99</td>
<td>85-99</td>
<td>15-20</td>
<td>CYP2D6, CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>60</td>
<td>&gt;99</td>
<td>4-10</td>
<td>2-3</td>
<td>CYP3A4, aldehyde oxidase</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Not available</td>
<td>&gt;99</td>
<td>48-68</td>
<td>14</td>
<td>CYP3A4, CYP2D6</td>
<td>Dehydro-aripiprazole</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>43-48</td>
<td>17</td>
<td>12</td>
<td>2-3</td>
<td>Not clinically relevant</td>
<td></td>
</tr>
</tbody>
</table>

1FMO, flavin-containing monooxygenase-3 system 2In italic and bold the most likely to have clinical relevance

**Risperidone** is extensively metabolized in the liver, primarily by 9-hydroxylation, yielding an active metabolite 9-hydroxyrisperidone (9-OH- risperidone) According to in vivo and in vitro studies, CYP2D6 and, to a lesser extent, CYP3A4 are responsible for the 9-hydroxylation of risperidone The metabolite 9-OH-risperidone is approximately equipotent with the parent drug in terms of dopamine receptor affinity and the total risperidone active moiety (sum of plasma concentrations of parent drug and metabolite) should contribute to the overall antipsychotic effect and side effects.

**Olanzapine** - The major metabolic pathways of olanzapine include direct N-glucuronidation, mediated by UGT1A4, and by N-demethylation, mediated by CYP1A2. Minor pathways of olanzapine biotransformation include N-oxidation, catalysed by flavin-containing monooxygenase-3 system, and 2-hydroxylation, metabolized by CYP2D6.

**Clozapine** has a complex hepatic metabolism in man with multiple CYP isoforms being involved in its biotransformation. The major metabolic pathways are the N-demethylation and the N-oxidation to form norclozapine, which has limited pharmacological activity, and clozapine N-oxide, respectively. Currently available in vitro and in vivo evidence clearly indicate that CYP1A2 plays a major role in the metabolism of clozapine, although other CYP isoforms, including CYP2C19, CYP2D6, CYP3A4 and CYP2C9, also contribute to its biotransformation.

### 2.12.1. Potential for Metabolic Drug Interactions of Antipsychotics and Clinical Relevance

(Spina E and Leon JD, 2007)

Concomitant administration of drugs acting as inhibitors or inducers of the enzymes involved in the biotransformation of the newer antipsychotics may decrease or increase their elimination. Plasma concentrations of the newer antipsychotics and/or their metabolites may therefore increase or decrease with subsequent clinical effects. For drugs such as olanzapine, whose major metabolic pathway is represented by glucuronidation, administration of CYP inhibitors will presumably result only in marginal changes. The addition of inducers can be problematic for all second-generation antipsychotics, but the decrease in plasma levels may be more dramatic for quetiapine, which is mainly dependent on CYP3A4.
Moreover, for compounds forming active metabolites, such as risperidone and aripiprazole, it will be necessary to consider the changes in both parent drug and active metabolite in the evaluation of the consequences of inhibitors or inducers. As previously mentioned, the clinical relevance of changes in plasma concentrations should be considered in view of the therapeutic index of the compound whose elimination is affected. In this respect, the newer antipsychotics have a wider therapeutic index as compared to traditional agents, at least with regard to extrapyramidal side effects. An exception is represented by risperidone that shows a dose- and concentration-dependent risk for parkinsonian symptoms at dosages above 6 mg/day. Moreover, compared to olanzapine, clozapine has a much narrower therapeutic index, and it is documented that central nervous system toxicity (e.g., generalized seizures, severe sedation, confusion and delirium) occurs more frequently at plasma concentrations above 1000 ng/ml.

The newer antipsychotics are involved in metabolic drug-drug interactions with other psychotropic agents or with compounds used in the treatment of concomitant somatic illnesses. Some of these interactions are well documented and may be clinically important, whereas others have been reported only anecdotally or reflect pharmacokinetic observations of doubtful practical relevance. In general, currently available novel antipsychotics do not affect the activity of major drug-metabolizing enzymes and consequently have minimal effects on the elimination of concomitantly given medications. On the other hand, drugs that inhibit or induce the CYP or UGT isoenzymes involved in metabolism of the various antipsychotic compounds may alter their plasma concentrations with subsequent risk of adverse effects or decreased efficacy. The therapeutic index of each atypical antipsychotic probably has major influence on the clinical significance of the interactions.

Table 6. Effect of various selective serotonin reuptake inhibitors (SSRI) on plasma concentrations of selected atypical antipsychotics: (Ref Spina E and Leon JD, 2007)

<table>
<thead>
<tr>
<th>SSRIs</th>
<th>Antipsychotic</th>
<th>Effect on plasma concentrations</th>
<th>Proposed mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Clozapine</td>
<td>Increase (40–70%)</td>
<td>Inhibition of various CYP isoforms (CYP2D6, CYP2C19 and CYP3A4)</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>Increase (75%)</td>
<td>Inhibition of CYP2D6 and, to a lesser extent, CYP3A4</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>No change or minimal increase</td>
<td>Inhibition of CYP2D6</td>
</tr>
<tr>
<td></td>
<td>Quetiapine</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Clozapine</td>
<td>Increase (20–40%)</td>
<td>Inhibition of CYP2D6</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>Increase (40–50%)</td>
<td>Inhibition of CYP2D6</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Clozapine</td>
<td>Increase (up to 5–10 times)</td>
<td>Inhibition of CYP1A2 and, to a lesser extent, CYP2C19 and CYP3A4</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>Minimal increase (10–20%)</td>
<td>Inhibition of CYP2D6 and CYP3A4</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>Increase (up to 100%)</td>
<td>Inhibition of CYP1A2</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Clozapine</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>Minimal increase</td>
<td>Inhibition of CYP2D6</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Citalopram/escitalopram</td>
<td>Clozapine</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>No change</td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Effect of various anti-epileptics on plasma concentrations of selected atypical antipsychotics:
(Ref Spina E and Leon JD, 2007)

<table>
<thead>
<tr>
<th>Antiepileptic</th>
<th>Antipsychotic</th>
<th>Effect on plasma concentrations</th>
<th>Proposed mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Clozapine</td>
<td>Decrease (50%)</td>
<td>Induction of CYP1A2, CYP3A4 and UGT</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Clozapine</td>
<td>Decrease (50-70%)</td>
<td>Induction of CYP3A4</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Clozapine</td>
<td>Decrease (10-70%)</td>
<td>Induction of CYP1A2 and UGT</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Clozapine</td>
<td>Decrease (80%)</td>
<td>Induction of CYP3A4</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Clozapine</td>
<td>Decrease (20-40%)</td>
<td>Induction of CYP3A4</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Clozapine</td>
<td>No change or minimal increase</td>
<td>Enzyme inhibition†</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Clozapine</td>
<td>No change</td>
<td>Enzyme inhibition†</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Clozapine</td>
<td>Increase (70-80%)</td>
<td>Protein displacement‡</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Clozapine</td>
<td>Decrease (20-30%)</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Clozapine</td>
<td>Decrease (30-40%)</td>
<td>Induction of CYP1A2, CYP3A4 and UGT</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Clozapine</td>
<td>No change</td>
<td>Induction of CYP3A4</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Olanzapine</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Quetiapine</td>
<td>Decrease (80%)</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Clozapine</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>Clozapine</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Risperidone</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Clozapine</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Risperidone</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Risperidone</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>No change</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CYP, cytochrome P450 monoxygenases; UGT, uridine diphosphate-glucuronosyltransferases

**Benzodiazepines**

Atypical antipsychotics are often used in combination with benzodiazepines. Apart from a specific potentiation of sedative effects, this combination is usually well tolerated. An exception may be clozapine. Within 24 or 48 hr after the first clozapine dose some patients taking benzodiazepines develop lethargy, ataxia, loss of consciousness and, rarely, respiratory arrest [107]. The respiratory arrest associated with the co-administration of benzodiazepines and clozapine appears to be an idiosyncratic reaction because many individuals can tolerate this combination, even in the first days of clozapine treatment, without any obvious side effects. However, it is safer to avoid benzodiazepines the week before starting clozapine and during the first week of dose titration.

There is no evidence of pharmacokinetic interactions between benzodiazepines and newer antipsychotics.

**H2-Antagonists**

Cimetidine is a wide spectrum inhibitor of several CYP isoenzymes and may therefore decrease the elimination of various drugs including atypical antipsychotics. However, other H2-antagonists, such as ranitidine and famotidine, do not interfere with the activity of the major drug-metabolizing enzymes and may therefore be co-administered safely with second-generation antipsychotics.

**Proton pump inhibitors**

Omeprazole is a proton pump inhibitor with an inducing effect on CYP1A2. Consistent with this, in two patients with schizoaffective disorder treated with clozapine at a daily dose of 325 mg, co-medication with omeprazole was associated with a more than 40% reduction in the plasma levels of clozapine.
**Fluoroquinolones**

Ciprofloxacin, a broad-spectrum fluoroquinolone antimicrobial, is a potent inhibitor of CYP1A2 and might therefore interfere with the elimination of those antipsychotics predominantly metabolized by this enzyme. Consistent with this, in a pharmacokinetic study of seven schizophrenic inpatients, concomitant administration of ciprofloxacin, 250 mg twice daily for 7 days, increased mean serum concentrations of clozapine and norclozapine by 29% and 31%, respectively. The possibility of a pharmacokinetic interaction between ciprofloxacin and olanzapine has been suggested by two case reports. The first report describes the case of a patient on stable treatment with olanzapine whose plasma antipsychotic concentration was almost doubled after the initiation of ciprofloxacin, 250 mg twice daily, suggesting the possibility of a metabolic interaction between these two drugs. In the second case, an elderly patient receiving a long-term treatment with olanzapine developed a marked QT interval prolongation after intravenous administration of ciprofloxacin.

**Macrolides**

Macrolide antibiotics, in particular erythromycin and troleandomycin are potent inhibitors of CYP3A4 and can interact adversely with substrates for this enzyme. Controversial findings have been reported concerning the interaction between erythromycin and clozapine. Two case reports have indicated that concomitant treatment with erythromycin resulted in an elevation of plasma clozapine levels, along with toxic effects such as somnolence, disorientation, dizziness, nausea and seizures. Conversely, in a study in 12 healthy volunteers, the pharmacokinetics of clozapine, administered as a single dose of 12.5 mg, were not significantly modified during co-administration with erythromycin, 1500 mg/day, suggesting a limited involvement of CYP3A4 in the metabolism of clozapine in humans. However, erythromycin steady-state was not reached in this study, and the doses of clozapine used were lower than those typically used in clinical practice. In 19 patients receiving quetiapine (200 mg, twice daily), co-administration with erythromycin (1500 mg/day) increased the half-life of quetiapine by 92% and decreased its clearance by 55%. In a study in 10 healthy volunteers who received a single 4-mg dose of sertindole, a novel antipsychotic partly metabolized by CYP3A4, concomitant administration of erythromycin, 250 mg taken orally four times daily, caused a small (15%), but significant increase in the Cmax of sertindole.

**Smoking**

Tobacco smoking is associated with induction of drug metabolizing enzymes, namely CYP1A2 and, possibly, UGTs, due to its by-products, in particular the polycyclic aromatic hydrocarbons. As a consequence, smoking may influence the elimination of those antipsychotics, such as clozapine and olanzapine, whose metabolism is mainly dependent on CYP1A2 and UGTs. In this respect, different studies have shown that plasma concentrations of clozapine (and its metabolite norclozapine) and olanzapine are lower, at the same dose, in smokers as compared to non-smokers. Concerning clozapine, the inducing effect of smoking was more evident in men than in women. Smoking cessation, if not accompanied by a dosage decrease, may be associated with increased plasma concentrations of these antipsychotics, possibly resulting in dose-related toxic effects. With regard to this, McCarty described the case of a patient on a stable clozapine dose who developed a myoclonic seizure and a generalized crisis a few weeks following sudden smoking cessation. Meyer has documented a mean increase of 72% in clozapine concentration in 11 patients following smoking withdrawal, with occurrence of unwanted effects in the patient showing the highest increase.
Caffeine

Caffeine may significantly inhibit clozapine metabolism, when taken in amounts between 400 and 1000 mg/day. Caffeine is metabolized by the same isoform, CYP1A2, primarily responsible for clozapine biotransformation. It is therefore likely that caffeine and clozapine compete for the same enzyme. As caffeine exhibits dose-dependent kinetics, clozapine elimination is generally decreased when caffeine is taken in moderate to elevated amounts. This interaction was first documented by Vainer and Choumard, who described a patient with side effects on clozapine after the addition of caffeine. A controlled study in patients with schizophrenia has documented an approximate 50% reduction of plasma clozapine concentrations after the removal of caffeine from the diet. In a recent investigation in 10 psychiatric patients, interestingly, instant coffee drinking elevated the mean serum clozapine concentrations by about 20% to 26%, compared to the decaffeinated phase. This increase was most probably a result of the inhibition of CYP1A2 by caffeine.

Grapefruit juice

Grapefruit juice can inhibit the activity of CYP3A4 in the intestine and in the liver and may elevate plasma concentrations of substrates for this isoform. With regard to this, plasma concentrations of clozapine and norclozapine were not affected by repeated ingestion of grapefruit juice. This confirms that enzymes other than CYP3A4, namely CYP1A2, play a major role in clozapine disposition. An increase in plasma levels of quetiapine, a CYP3A4 substrate, is likely to occur following grapefruit juice ingestion, but it has not been documented.

2.13. Therapeutic Uses of Antipsychotics (Katzung BG, Masters SB & Trevor AJ, 2012)

a) Psychiatric Indications

Schizophrenia is the primary indication for antipsychotic agents. Antipsychotic drugs are also used very extensively in patients with psychotic bipolar disorder (BP1), psychotic depression, and treatment resistant depression.

Catatonic forms of schizophrenia are best managed by intravenous benzodiazepines. After catatonia has ended, antipsychotic drugs may be needed to treat psychotic components of that form of the illness, and remain the mainstay of treatment for this condition. Unfortunately, many patients show little response, and virtually none show a complete response.

Antipsychotic drugs are also indicated for schizoaffective disorders, which share characteristics of both schizophrenia and affective disorders. No fundamental difference between these two diagnoses has been reliably demonstrated. They are part of a continuum with bipolar psychotic disorder. The psychotic aspects of the illness require treatment with antipsychotic drugs, which may be used with other drugs such as antidepressants, lithium, or valproic acid. The manic phase in bipolar affective disorder often requires treatment with antipsychotic agents, although lithium or valproic acid supplemented with high-potency benzodiazepines (e.g., lorazepam or clonazepam) may suffice in milder cases. Recent controlled trials support the efficacy of monotherapy with atypical antipsychotics in the acute phase (up to 4 weeks) of mania, and olanzapine and quetiapine has been approved for this indication. As mania subsides, the antipsychotic drug
may be withdrawn, although maintenance treatment with atypical antipsychotic agents has become more common. Nonmanic excited states may also be managed by antipsychotics, often in combination with benzodiazepines.

Other indications for the use of antipsychotics include Tourette’s syndrome, disturbed behavior in patients with Alzheimer’s disease, and, with antidepressants, psychotic depression. Antipsychotics are not indicated for the treatment of various withdrawal syndromes, e.g., opioid withdrawal. In small doses, antipsychotic drugs have been promoted (wrongly) for the relief of anxiety associated with minor emotional disorders. The antianxiety sedatives are preferred in terms of both safety and acceptability to patients.

b) Nonpsychiatric Indications
Most older typical antipsychotic drugs, with the exception of thioridazine, have a strong antiemetic effect. This action is due to dopamine-receptor blockade, both centrally (in the chemoreceptor trigger zone of the medulla) and peripherally (on receptors in the stomach). Some drugs, such as prochlorperazine and benzoquinamide, are promoted solely as antiemetics.

Phenothiazines with shorter side chains have considerable H1-receptor-blocking action and have been used for relief of pruritus or, in the case of promethazine, as preoperative sedatives. The butyrophenone droperidol is used in combination with an opioid, fentanyl, in neuroleptanesthesia.

2.14. Unwanted Effects of Atypical Antipsychotics
Although atypical antipsychotic agents share the clinical attributes of a broader spectrum of efficacy, and lower risk of EPS and TD, these agents are chemically and pharmacologically distinct from one another, and each consequently has a unique side effect profile.

Table 8 (Tandon et al, 2008)

<table>
<thead>
<tr>
<th></th>
<th>Ziprasidone</th>
<th>Aripiprazole</th>
<th>Haloperidol</th>
<th>Clozapine</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS</td>
<td>0 to +</td>
<td>0 to +</td>
<td>+++</td>
<td>0</td>
<td>0 to ++</td>
<td>0 to +</td>
<td>0</td>
</tr>
<tr>
<td>Metabolic</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+ to ++</td>
<td>+++</td>
<td>+ to ++</td>
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<tr>
<td>TD</td>
<td>0 to +</td>
<td>0 to +</td>
<td>+++</td>
<td>0</td>
<td>0 to +</td>
<td>0 to +</td>
<td>0 to +</td>
</tr>
<tr>
<td>Prolactin elevation</td>
<td>±</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td>±</td>
<td>0</td>
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<tr>
<td>Anticholinergic</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>+++</td>
<td>±</td>
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<td>±</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>++</td>
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<td>±</td>
</tr>
<tr>
<td>Hypotension</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Sedation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Weight gain</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>

0—absent, ±—minimal, +—mild, ++—moderate, +++—severe, AST/ALT—aspartate aminotransferase/alanine aminotransferase. EPS—extrapyramidal side effects, TD—tardive dyskinesia (Adapted from Tandon et al [12*])

Antipsychotic drugs produce two main kinds of motor disturbance in humans: acute dystonias and tardive dyskinesias, collectively termed extrapyramidal side effects. These all result directly or indirectly from D₂ receptor blockade in the nigrostriatal pathway. Extrapyramidal side effects constitute one of the main disadvantages of first-generation antipsychotic drugs. The term atypical was originally applied to some of the newer compounds that show much less tendency to produce extrapyramidal side effects.

Table 9. Extrapyramidal Motor Disturbances (Brunton LL, Chabner BA and Knollmann BC, 2011)

<table>
<thead>
<tr>
<th>NEUROLOGICAL SIDE EFFECT</th>
<th>FEATURES</th>
<th>TIME OF ONSET AND RISK INFO</th>
<th>PROPOSED MECHANISM</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute dystonia</td>
<td>Spasm of muscles of tongue, face, neck, back</td>
<td>Time, 1-5 days Young, antipsychotic naive patients at highest risk</td>
<td>Acute DA antagonism</td>
<td>Anti-parkinsonian agents are diagnostic and curative³</td>
</tr>
<tr>
<td>Akathisia</td>
<td>Subjective and objective restlessness, not anxiety or &quot;agitation&quot;</td>
<td>Time 5-60 days Unknown</td>
<td>Reduce dose or change drug, clonazepam, propranolol more effective than anti-parkinsonian agents⁵</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Bradykinesia, rigidity, variable tremor, mask facies, shuffling gait</td>
<td>Time 5-30 days Elderly at greatest risk</td>
<td>DA antagonism</td>
<td>Dose reduction, change medication, anti-parkinsonian agents⁵</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome</td>
<td>Extreme rigidity, fever, unstable BP, myoglobinemia, can be fatal</td>
<td>Time weeks–months Can persist for days after stopping antipsychotic</td>
<td>DA antagonism</td>
<td>Stop antipsychotic immediately, supportive care, dantrolene and bromocriptine⁶</td>
</tr>
<tr>
<td>Perioral tremor (&quot;rabbit syndrome&quot;)</td>
<td>Perioral tremor [may be a late variant of parkinsonism]</td>
<td>Time months or years of treatment Unknown</td>
<td>Anti-parkinsonian agents often help⁶</td>
<td></td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>Orofacial dyskinesia, rarely widespread choreoathetosis or dystonia</td>
<td>Time, months, years of treatment Elderly at 5-fold greater risk Risk of D₂ blockade</td>
<td>Postsynaptic DA receptor supersensitivity, up-regulation</td>
<td>Prevention crucial, treatment unsatisfactory May be reversible with early recognition and drug discontinuation</td>
</tr>
</tbody>
</table>

*Treatment diphenhydramine 25-50 mg IM, or benztropine 1-2 mg IM Due to long antipsychotic half-life, may need to repeat, or follow with oral medication ⁴Propranolol often effective in relatively low doses (20-80 mg/day in divided doses) Selective adrenergic receptor antagonists are less effective Non-lipophilic adrenergic antagonists have limited CNS penetration and are of no benefit (e.g., atenolol) ⁶Use of amantadine avoids anticholinergic effects of benztropine or diphenhydramine. Despite the response to dantrolene, there is no evidence of abnormal Ca²⁺ transport in skeletal muscle, with persistent antipsychotic effects (e.g., long-acting injectable agents), bromocriptine may be tolerated in large doses (10-40 mg/day). Anti-parkinsonian agents are not effective.

It appears that rates of Neuroleptic Malignant Syndrome and Tardive Dyskinesia are lower with newer-generation in contrast with conventional antipsychotic agents. (Tandon & Jibson, 2003)
**EPS-Underlying Mechanism:** Drugs that rapidly dissociate from D₂ receptors (e.g., clozapine, olanzapine, sertraline) induce less severe extrapyramidal side effects. A possible explanation for this is that with a rapidly dissociating compound, a brief surge of dopamine can effectively overcome the block by competition, whereas with a slowly dissociating compound, the level of block takes a long time to respond to the presence of endogenous dopamine, and is in practice non-competitive. Adverse motor effects may be avoided if fractional receptor occupation falls during physiological surges of dopamine. An extension of this idea is that perhaps a little D₂ receptor activation may be beneficial. This could be produced, for example, by drugs that are D₂ partial agonists (e.g., aripiprazole) in contrast to simple antagonists. It is thought that partial agonists reduce D₂ hyperactivation in the mesolimbic pathway, thus alleviating positive symptoms of schizophrenia, but provide enough D₂ receptor stimulation in the mesocortical pathway to prevent negative symptoms, and in the nigrostriatal pathway to prevent the development of extrapyramidal side effects. Newer D₂ partial agonists such as bifeprunox are being developed, although questions about their efficacy and safety have arisen (Rang HP et al., 2011).

By definition, all atypical antipsychotics are less likely than typical antipsychotics to cause EPS; in fact, that is how they got the atypical label. Among newer-generation antipsychotics, the hierarchy of EPS risk is risperidone > olanzapine = ziprasidone = aripiprazole > quetiapine > clozapine. Clinically, these differences are most relevant in vulnerable populations, such as the elderly, adolescents, and patients with Parkinson's disease with psychosis (Tandon and Jibson, 2003).

Based on D₂ receptor binding affinity, Seeman and Tallerico (1998) concluded that those antipsychotics such as risperidone that elicit movement disorders bind more tightly to D₂ receptors, whereas antipsychotics such as olanzapine and clozapine that elicit few or no movement disorders bind loosely to D₂ receptors and dissociate more rapidly (Maguire GA, 2002).

Treatment-emergent extrapyramidal side effects are among important measures of assessing tolerability of antipsychotic agents. Rates of patients experiencing extrapyramidal side effects and measures of severity of symptoms were not found to be different among the drugs in most trials. Small numbers of studies found worse extrapyramidal side effect outcomes with risperidone compared with olanzapine, clozapine, or quetiapine, although the specific measures on which risperidone performed worse were not consistent across these studies. Clozapine and ziprasidone were also found to have worse outcomes than olanzapine on a limited number of outcomes in a few trials (McDonagh et al., 2010).
In 12 week-long prospective naturalistic observational study comparing risperidone (n=38), olanzapine (n=38) and clozapine in inpatients and outpatients, Strous R D et al (2006) observed that only individuals receiving clozapine indicated improvement in tardive dyskinesia [as expressed in AIMS (Abnormal Involuntary Movement Scale) scores] over the course of the study. No differences were noted between the three subgroups regarding effects on Parkinsonism or akathisia suggesting that all three demonstrate similar effects, or lack thereof, on these ubiquitous adverse effects of antipsychotic medications, commonly observed with typical antipsychotic medications.

In CATIE Phase I Study, differences were not found between olanzapine, quetiapine, risperidone, or ziprasidone in the incidence of extrapyramidal symptoms identified as an adverse event or akathisia or movement disorders based on rating scales. Similarly, differences were not found between drugs in the subsequent CATIE Phase Ib, Phase IIE, or Phase IIT nor in another trial with multiple drugs (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone (McDonagh et al., 2010).

Four studies comparing clozapine with olanzapine assessed extrapyramidal symptoms. One found a difference when comparing the mean change in SAS (Simpson Angus Scale) score from baseline to endpoint (-1.4 for clozapine, -3.2 for olanzapine). Other measures of extrapyramidal symptoms were not different between the drugs in this trial. Mean doses in this trial were lower than midpoint for clozapine and within midrange for olanzapine, which may have had an impact on these results. The other studies found no differences between the drugs in extrapyramidal symptoms outcomes (McDonagh et al., 2010).

For all other comparisons made in head-to-head trials, at least some differences were found. Of 10 studies of olanzapine and risperidone (2223 patients total) reporting extrapyramidal symptom adverse event data, 8 found no differences between the drugs while 2 (586 patients total) found risperidone to have higher rates or worsening symptoms of extrapyramidal symptoms on measures reflecting akathisia, dyskinesia, dystonia, pseudoparkinsonism, and overall extrapyramidal symptoms. Mean doses of risperidone 5 and 7 mg were compared with olanzapine 13 and 17 mg of olanzapine, respectively. Across these studies, size and quality ratings were similar. One good-quality, short-term trial (N=377) was statistically powered to determine a difference in extrapyramidal adverse event reports and found no differences between the groups on this measure or on Extrapyramidal Symptom Rating Scale (ESRS) scores or use of anticholinergic medications. In this trial the mean dose of olanzapine was below midrange, while the mean dose of risperidone was near the midpoint (5 mg). The other good-quality trial found treatment-emergent and worsening pre-existing extrapyramidal symptoms in 28.9% (N=35) of olanzapine patients and 50.4% (N=61) of risperidone patients (P=0.0006). Dosing in this study also had olanzapine slightly below midrange and risperidone within midrange (McDonagh et al., 2010).
In the general schizophrenia patient population, clozapine has low risk of EPS across its entire dose range, whereas the incidence of EPS in risperidone and olanzapine is dose related (Juncos J, 2000). In present study, the dosing pattern used in study participants (n=154) - in risperidone group at baseline was 4.39 (range 2.00–8.00, SD 1.28) mg and at endpoint was 4.76 (range 1.00–8.00, SD 1.50), in olanzapine group at baseline was 12.78 (range 5.00–20.00, SD 3.01) mg and at was endpoint 13.19 (range 5.00–20.00, SD 3.90); and in clozapine group at baseline was 260.00 (range 200.00–300.00, SD 54.77) mg and at endpoint was 240.00 (range 200.00–300.00, SD 54.77).

2.14.2. Sedation
It is the most common single side effect of antipsychotic medications. Antihistamine (H1) activity is a property of some phenothiazine antipsychotics (e.g., chlorpromazine and methotrimeprazine) and contributes to their sedative and antiemetic properties, but not to their antipsychotic action. Sedation is most prominent in the early stages of antipsychotic therapy, and some degree of tolerance develops over time with continued administration. Lowering of the daily dose, consolidation of divided doses into one evening dose, or changing to a less sedating antipsychotic medication can be helpful.

All newer-generation antipsychotics and conventional agents are sedating (hence the old term tranquilizer), but they all cause different degrees of sedation. Among the newer generation agents, the hierarchy of producing sedation is (Tandon & Jibson, 2003)

\[
\text{clozapine} > \text{quetiapine} > \text{olanzapine} > \text{risperidone} > \text{ziprasidone} = \text{aripiprazole}
\]

2.14.3. Seizures
Though recognized as a complication of chlorpromazine treatment, were so rare with the high-potency older drugs as to merit little consideration. However, de novo seizures may occur in 2–5% of patients treated with clozapine. Use of an anticonvulsant is able to control seizures in most cases. (Katzung BG, Masters SB & Trevor AJ, 2012)

2.14.4. Autonomic Nervous System Effects
All antipsychotic drugs block a variety of receptors, particularly acetylcholine (muscarinic), histamine (H1), noradrenaline (α) and 5-HT.

The peripheral anticholinergic (antimuscarinic) effects of antipsychotic medications include dryness of mouth, blurring of vision, constipation, tachycardia, and urinary retention. Most patients are able to tolerate the antimuscarinic adverse effects of antipsychotic drugs. These side effects can be particularly troublesome for older patients. Those who are made too uncomfortable or who develop urinary retention or other severe symptoms can be switched to an agent without significant antimuscarinic action.
Central anticholinergic effects can lead to impaired memory and cognition, confusion, delirium, somnolence, and hallucinations. Such symptoms are more likely to occur with medications that have more potent anticholinergic effects and in elderly or medically debilitated patients. However, anticholinergic (antimuscarinic) effects may also be beneficial in relation to extrapyramidal side effects.

Among the newer-generation antipsychotic agents, the hierarchy of anticholinergic side effects is as follows:

\[
\text{clozapine} > \text{olanzapine} > \text{quetiapine} \geq \text{risperidone} = \text{ziprasidone} = \text{aripiprazole}
\]

It should be noted, however, that except for clozapine, the magnitude of anticholinergic side effects associated with the atypicals is much smaller than that associated with benztropine and trihexyphenidyl (oral anticholinergic agents used to prevent and treat antipsychotic-associated EPS). It is therefore critical that EPS be avoided without concomitant use of anticholinergic agents (Tandon & Jibson, 2003).

Blocking of \( \alpha \)-adrenoceptors causes orthostatic hypotension. Orthostatic hypotension or impaired ejaculation—These common complications of therapy with chlorpromazine or mesoridazine are managed by switching to drugs with less marked adrenoceptor-blocking actions (Katzung BG and others, 2012). Tachycardia can result from the anticholinergic effects of antipsychotic medications but may also occur as a result of postural hypotension. The elderly are particularly prone to this adverse effect.

All antipsychotic agents cause hypotension, particularly postural hypotension, although they do so to different extents. Among the newer-generation antipsychotics, the hierarchy of producing hypotension is:

\[
\text{clozapine} > \text{quetiapine} > \text{risperidone} > \text{olanzapine} = \text{ziprasidone} = \text{aripiprazole}
\]

Hypotension tends to be most prominent in the early stages of treatment, with tolerance developing over time. Adequate hydration mitigates the problem of hypotension, although agents that are associated with more hypotension are best titrated up to their target dose (over 2–3 days for risperidone and quetiapine, and over 1–2 weeks for clozapine) (Tandon & Jibson, 2003).

2.14.5. Metabolic and Endocrine Effects

Galactorrhoea and oligomenorrhea. Dopamine, released in the median eminence by neurons of the tuberohypophyseal pathway, acts physiologically via \( D_2 \) receptors to inhibit prolactin secretion. Blocking \( D_2 \) receptors by antipsychotic drugs can therefore increase the plasma prolactin concentration, resulting in breast swelling, pain and lactation, which can occur in men as well as in women.

Among the newer-generation agents, risperidone alone consistently increases prolactin levels. Whereas clozapine, quetiapine, olanzapine, and ziprasidone do not cause any sustained increase in prolactin levels, aripiprazole actually causes a modest decrease because of its partial agonist activity at the dopamine \( D_2 \)
It is suggested that prolactin-related clinical side effects occur in about 25% to 30% of patients with increased levels of prolactin (Tandon & Jibson, 2003).

Risperidone can produce hyperprolactinemia comparable to that caused by typical compounds, whereas clozapine does not elevate prolactin beyond normal levels. The resultant hyperprolactinemia can lead to galactorrhea (secretion of liquid from the nipples) in 1% to 5% of patients and menstrual cycle changes (e.g., oligomenorrhea) in up to 20% of women.

In a 4-week nonrandomized open-label observational study, Westheide J et al (2008) in 102 in-patients with schizophrenia examined the sexual functioning, subjective well-being, endocrinological parameters as well as psychopathological characteristics. It was reported that increased prolactin levels do not seem to be decisive for antipsychotic induced sexual dysfunction. However, improvement of severity of illness and regaining the ability to regulate one’s own emotion have positive influence on sexual functioning.

**Based on D₂ receptor affinity the relative potency of antipsychotic agents in elevating serum prolactin is:**

Risperidone = Paliperidone > Haloperidol > Olanzapine > Ziprasidone > Quetiapine > Clozapine > Aripiprazole (Carlson HE, 2007)

Weight gain is a common and troublesome side effect. Increased risk of diabetes occurs with several atypical antipsychotic drugs. These effects are probably related to their antagonist actions at H₁, 5-HT and muscarinic receptors. Treatment with at least some SGAs and phenothiazines appears associated with elevations in serum triglycerides and cholesterol.

### 2.14.6. Other Unwanted Effects of Atypical Antipsychotics

Increased risk of cardiovascular disease occurs with several atypical antipsychotic drugs. These effects are probably related to their antagonist actions at H₁, 5-HT and muscarinic receptors.

**a) Effects on sexual function**

Disturbances in sexual function can occur. Erectile dysfunction occurs in 23%-54% of men. Other effects can include ejaculatory disturbances in men and loss of libido or anorgasmia in women and men. In addition, with specific antipsychotic medications, including thioridazine and risperidone, retrograde ejaculation has
b) Ophthalmic effects, Pigmentary retinopathies and Corneal opacities

The blockade of muscarinic receptors produces increased intraocular pressure. Deposits in the anterior portions of the eye (cornea and lens) are a common complication of chlorpromazine therapy. They may accentuate the normal processes of aging of the lens. Thioridazine is the only antipsychotic drug that causes retinal deposits, which in advanced cases may resemble retinitis pigmentosum. The deposits are usually associated with "browning" of vision. The maximum daily dose of thioridazine has been limited to 800 mg/d to reduce the possibility of this complication. (Katzung BG and others, 2012) For this reason, patients maintained with these medications should have periodic ophthalmic examinations.

c) Idiosyncratic and hypersensitivity reactions can occur, the most important being the following: (Rang HP et al, 2011)

- **Jaundice**, which occurs with older phenothiazines such as chlorpromazine. The jaundice is usually mild, associated with elevated serum alkaline phosphatase activity (an 'obstructive' pattern), and disappears quickly when the drug is stopped or substituted by a chemically unrelated antipsychotic.

- **Leukopenia and agranulocytosis** are rare but potentially fatal, and occur in the first few weeks of treatment. The incidence of leukopenia (usually reversible) is less than 1 in 10,000 for most antipsychotic drugs, but much higher (1-2%) with clozapine, whose use therefore requires regular monitoring of blood cell counts. Provided the drug is stopped at the first sign of leukopenia or anaemia, the effect is reversible. Olanzapine appears to be free of this disadvantage.

- **Urticarial skin reactions** are common but usually mild. Excessive sensitivity to ultraviolet light may also occur.

- **Photosensitivity** also occurs infrequently and is most common with the low-potency phenothiazine medications, patients should be instructed to avoid excessive sunlight and/or use sunscreen.

- **Neuroleptic malignant syndrome** is a rare but serious complication similar to the malignant hyperthermia syndrome seen with certain anaesthetics. Muscle rigidity is accompanied by a rapid rise in body temperature and mental confusion. It is usually reversible, but death from renal or cardiovascular failure occurs in 10-20% of cases.

2.14.7. Use in Pregnancy

Although antipsychotic drugs appear to be relatively safe in pregnancy, a small increase in teratogenic risk could be missed. Questions about whether to use these drugs during pregnancy and whether to abort a pregnancy in which the fetus has already been exposed must be decided individually. If a pregnant woman...
could manage to be free of antipsychotic drugs during pregnancy, this would be desirable because of their effects on the neurotransmitters involved in neurodevelopment. (Katzung BG, Masters SB & Trevor AJ, 2012)

2.14.8. Toxicity with Overdose
Overdoses with antipsychotics are rarely fatal unless they are complicated by pre-existing medical problems or concurrent ingestion of alcohol or other medications. Acute overdose with antipsychotics rarely results in serious symptomatology. Mild intoxication manifests as sedation, hypotension, and miosis; whereas with severe intoxication, agitation and delirium can typically progress to motor retardation, seizures, cardiac arrhythmias, respiratory arrest, and coma. Dystonias and pseudoparkinsonism symptoms also occur. Supportive measures, gastric lavage, and activated charcoal are recommended. Induction of emesis can be difficult because of effects on the chemoreceptor trigger zone, and dialysis is ineffective because of the degree of drug-protein binding. Phenytoin or sodium bicarbonate are useful in the treatment of quinidine-like cardiac conduction effects on the QRS or QTc. Physostigmine is not generally recommended to reverse anticholinergic toxicity because of deleterious effects on arrhythmias and seizure threshold. (Dipiro JT and others, 2011)

2.15. Treatment of Schizophrenia with Antipsychotics
2.15.1. Phases of Treatment in schizophrenia (Sadock BJ, Sadock VA & Ruiz P 2009)
Pharmacologic treatment differs depending on the phase of a patient's illness.

The 'acute stage' is usually characterized by psychotic symptoms that require immediate clinical attention. These symptoms may represent a first psychotic episode or, more commonly, a relapse in an individual who has experienced multiple prior episodes. Treatment during this phase focuses on alleviating the most severe psychotic symptoms. The acute phase usually lasts from 4 to 8 weeks.

Following the acute phase, patients usually enter a stabilization phase in which acute symptoms are controlled, but patients remain at risk for relapse if treatment is interrupted or if the patients are exposed to stress. During this phase, treatment focuses on consolidating therapeutic gains, with similar treatments as those used in the acute stage. This phase may last as long as 6 months following recovery from acute symptoms.

The third stage is the 'stable or maintenance phase' when the illness is either in a relative stage of remission or symptomatically stable. The goals during this phase are to prevent psychotic relapse or exacerbation and to assist patients in improving their level of functioning.
Poor Responders When patients with acute schizophrenia are administered an antipsychotic medication, approximately 50 percent will improve to the extent that they will achieve a complete remission or experience only mild symptoms. The remaining 50 percent of patients will improve, but will still demonstrate variable levels of positive symptoms that are resistant to the medications. Rather than categorizing patients into responders and nonresponders, it is more accurate to consider the degree to which the illness is improved by medication. Some patients are so severely ill that they require chronic institutionalization. Others will respond to an antipsychotic with substantial suppression of their psychotic symptoms, but will demonstrate persistent symptoms such as hallucinations or delusions.

2.15.2. Choice of Antipsychotic in Schizophrenia (Katzung BG, Masters SB & Trevor AJ, 2012)
Choice among antipsychotic drugs in schizophrenia is based mainly on differences in adverse effects and possible differences in efficacy. Since use of the older drugs is still widespread, especially for patients treated in the public sector, knowledge of such agents as chlorpromazine and haloperidol remains relevant. Thus, one should be familiar with one member of each of the three subfamilies of phenothiazines, a member of the thioxanthene and butyrophenone group, and all of the newer compounds—clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. Each may have special benefits for selected patients.

There are various detailed Treatment/Prescribing Guidelines for Schizophrenia such as –
- NICE (National Institute For Clinical Excellence, Guidance on the Use of Newer (Atypical) Antipsychotic Drugs for the Treatment of Schizophrenia, 2002),
- Patient Outcomes Research Team (PORT) treatment recommendations
- Texas Medication Algorithm Project (TMAP) (Fig. 21) (Argo TR et al, 2008)
- World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia
- Canadian Psychiatric Association’s Clinical Practice Guidelines - Treatment of Schizophrenia
Fig. 21. Algorithm for the Treatment of Schizophrenia Recommended by TMAP: (Fig: Argo TR et al, 2008)

**Stage 1**
- *First episode patients usually require lower antipsychotic dosing and should be closely monitored due to greater sensitivity to medication side effects. Lack of consensus on inclusion of FGAs as option for first episode.*

**Stage 2**
- **Partial or Nonresponse**
- **Trial of a single SGA (ARIPIPRAZOLE, OLanzAPINE, QUETIAPINE, Risperidone, or ZIPRASIDONE)***
- **Partial or Nonresponse**
- **Trial of a single SGA or FGA (not SGA tried in Stage 1)**

**Stage 3**
- **CLOzapine**
- **Partial or Nonresponse***

**Stage 4**
- **CLOzapine**
- **(FGA, SGA or ECT)**
- Inconsistent results in RCTs
- Nonresponse
- **Value in clozapine failures not established**

**Stage 5**
- **Trial of a single agent FGA or SGA (not tried in Stages 1 or 2)**
- Nonresponse
- **Combination Therapy**
  - E.g. SGA + FGA, combination of SGAs, (FGA or SGA) + ECT, (FGA or SGA) + other agent (e.g. mood stabilizer)**

**Stage 6**
- Nonresponse
- **Case reports, no controlled studies of combinations in long-term treatment of schizophrenia**

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a) **Acute (Short-Term) Treatment** (Brunton LL, Chabner BA and & Knollmann BC, 2011)

The immediate goals of acute antipsychotic treatment are the reduction of agitated, disorganized, or hostile behavior, decreasing the impact of hallucinations, the improvement of organization of thought processes, and the reduction of social withdrawal. Doses used are often higher than those required for maintenance treatment of stable patients.

Newer, atypical antipsychotic agents do offer a better neurological side-effect profile than typical antipsychotic drugs. Clinically effective doses of atypical agents show markedly reduced EPS risk (or nearly absent in the case of quetiapine and clozapine) compared to typical antipsychotic agents. Excessive D2...
blockade, as is often the case with the use of high-potency typical agents (e.g., haloperidol), not only increases risk for motor neurological effects (e.g., muscular rigidity, bradykinesia, tremor, akathisia), but also slows mentation (bradyphrenia), and interferes with central reward pathways, resulting in patient complaints of anhedonia. Rarely used are low-potency typical agents (e.g., chlorpromazine), which also have high affinities for H1, M, and α1 receptors that cause many undesirable effects (sedation, anticholinergic properties, orthostasis). Concerns regarding QTc prolongation (e.g., thioridazine) further limit their clinical usefulness. In acute psychosis, sedation may be desirable, but the use of a sedating antipsychotic drug may interfere with a patient’s cognitive function and social reintegration. Clinicians often prefer using non-sedating antipsychotic agents, and add low doses of benzodiazepines as necessary. As a result of the improved neurological risk profile and aggressive marketing, atypical antipsychotic agents have essentially replaced typical antipsychotic drugs in clinical practice. Despite considerable debate, newer atypical antipsychotic agents are not more effective in the treatment of positive symptoms than typical agents (Rosenheck et al., 2006; Sikich et al., 2008), there may be small but measurable differences in effects on negative symptoms and cognition (Leucht et al., 2009).

b) Long-Term Treatment (Brunton LL, Chabner BA and Knollmann BC, 2011)
The need for long-term treatment poses issues almost exclusively to the chronic psychotic illnesses, schizophrenia and schizoaffective disorder, although long-term antipsychotic treatment is sometimes used for manic patients, for ongoing psychosis in dementia patients, for L-dopa psychosis, and for adjunctive use in SSRI-unresponsive major depression. Safety concerns combined with limited long-term efficacy data have dampened enthusiasm for extended antipsychotic drug use in dementia patients (Jeste et al., 2008). The goal should be to optimize clinical and behavioral aspects of treatment in order to minimize the need for antipsychotic drugs in the dementia population. Justification for ongoing use, based on documentation of patient response to tapering of antipsychotic medication, is often mandated in long-term care settings. L-dopa psychosis represents a thorny clinical problem, as clinicians are caught between the dilemma of treatment-induced psychotic symptoms and the motoric worsening as a result of exposure to antipsychotic drugs. Parkinson disease patients who present with L-dopa psychosis usually have advanced disease and cannot tolerate reductions in dopamine agonist treatment without significant motoric worsening and on-off phenomena. They are exquisitely sensitive to minute amounts of D2 blockade (Zahodne and Fernandez, 2008). Clozapine, used in doses ranging from 6.25-50 mg/day, has the most extensive clinical evidence base. The necessity for routine hematological monitoring for agranulocytosis has prompted the use of low doses of quetiapine, itself a very weak D2 antagonist, although the evidence for quetiapine’s efficacy in L-dopa psychosis is not compelling. Anecdotal evidence also exists for using low doses of the D2 partial agonist aripiprazole (1-5 mg/day) in L-dopa psychosis (Zahodne and Fernandez, 2008).
The choice of antipsychotic agents for long-term schizophrenia treatment is based primarily on avoidance of adverse effects and, when available, prior history of patient response. Since schizophrenia spectrum disorders are lifelong diseases, treatment acceptability is paramount to effective illness management. Whether atypical antipsychotic agents are superior to typical antipsychotic agents has been the subject of significant and contentious debate.

Large meta-analyses of predominantly industry-funded studies find only minute differences in relapse risk (Leucht et al., 2003). Atypical antipsychotic agents offer significant advantages related to reduced neurological risk, with long-term tardive dyskinesia rates < 1%, or approximately one-fifth to one-tenth of that seen with typical antipsychotic drugs (for haloperidol, the annual incidence of tardive dyskinesia is 4-5% in non-geriatric adult patients; lifetime risk ~20%). This advantage of the atypical agents is magnified in elderly patients, in whom tardive dyskinesia incidence is 5-fold greater than in younger patients, and for whom annual tardive dyskinesia rates with typical antipsychotic agents exceed 20% per year. The decreased affinity for D2 receptors among atypical agents has also translated into reduced concerns over hyperprolactinemia with most atypical antipsychotic agents, although risperidone and paliperidone (9-OH risperidone) are exceptions; both agents cause dose-dependent increases in prolactin.

While concerns over EPS and tardive dyskinesia have abated with the introduction of the atypical antipsychotic agents into clinical practice, there has been increased concern over metabolic effects of antipsychotic treatment—weight gain, dyslipidemia (particularly hypertriglyceridemia), and an adverse impact on glucose-insulin homeostasis, including new-onset type 2 DM, and diabetic ketoacidosis (DKA), with reported fatalities from the latter (ADA-APA-AACE-NAASO, 2004). Clozapine and olanzapine have the highest metabolic risk and are only used as last resort. Olanzapine has been relegated in most treatment algorithms to third-tier status, and is considered only after failure of more metabolically benign agents such as aripiprazole, ziprasidone, asenapine, iloperidone, risperidone, and paliperidone.

Acutely psychotic patients usually respond within hours after drug administration, but weeks may be required to achieve maximal drug response, especially for negative symptoms, which respond much less robustly to drug therapy. While 6 weeks of therapy has been considered an adequate antipsychotic trial, analyses of symptom response in clinical trials indicate that the majority of response to any antipsychotic treatment in acute schizophrenia is seen by week 4 (Agid et al., 2003, Emsley et al., 2006). Failure of response after 2 weeks should prompt a clinical reassessment, including determination of medication adherence, before a decision is made to increase the current dose or consideration of switching to another agent. First-episode schizophrenia patients often respond to modest doses, and more chronic patients may require doses that exceed recommended ranges. While the acute behavioral impact of treatment is seen within hours to
Review of Literature

days, long-term studies indicate improvement may not plateau for 6 months, underscoring the importance of ongoing antipsychotic treatment in functional recovery for schizophrenia patients.

Usual dosages for acute and maintenance treatment are noted in below-given table. Dosing should be adjusted based on clinically observable signs of antipsychotic benefit and adverse effects. For example, higher EPS risk is noted for risperidone doses that exceed 6 mg/day in non-elderly adult schizophrenia patients. However, in the absence of EPS, increasing the dose from 6-8 mg would be a reasonable approach in a patient with ongoing positive symptoms, albeit with appropriate monitoring for emerging EPS symptoms.

Treatment-limiting adverse effects may include weight gain, sedation, orthostasis, and EPS, which to some degree can be predicted based on the potencies of the selected agent to inhibit neurotransmitter receptor. The detection of dyslipidemia or hyperglycemia is based on laboratory monitoring. Certain adverse effects such as hyperprolactinemia, EPS, orthostasis, and sedation may respond to dose reduction, but metabolic abnormalities improve only with discontinuation of the offending agent and a switch to a more metabolically benign medication. The decision to switch stable schizophrenia patients with antipsychotic-related metabolic dysfunction solely for metabolic benefit must be individualized, based on patient preferences, severity of the metabolic disturbance, likelihood of metabolic improvement with antipsychotic switching, and history of response to prior agents. Patients with refractory schizophrenia on clozapine are not good candidates for switching because they are resistant to other medications.
Table 10. Antipsychotic Drugs - Dosage

<table>
<thead>
<tr>
<th>ANTIPSYCHOTIC</th>
<th>DOSAGE FORMS</th>
<th>ORAL DOSAGE (mg/day)</th>
<th>METABOLIC SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ACUTE PSYCHOSIS</td>
<td>MAINTENANCE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st Episode</td>
<td>Chronic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st Episode</td>
<td>Chronic</td>
</tr>
</tbody>
</table>

**TYPICAL ANTIPSYCHOTIC AGENTS**

**(A) Phenothiazines**

<table>
<thead>
<tr>
<th>NON-PROPRIETARY NAME</th>
<th>DOSAGE FORMS</th>
<th>ACUTE PSYCHOSIS</th>
<th>MAINTENANCE</th>
<th>METABOLIC SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>O, S, IM</td>
<td>200-600</td>
<td>400-800</td>
<td>150-600</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250-750</td>
<td></td>
<td>+++</td>
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<td></td>
<td></td>
<td>250-750</td>
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<td>+++</td>
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<tr>
<td></td>
<td></td>
<td>250-750</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>O, S, IM</td>
<td>12-50</td>
<td>24-48</td>
<td>12-48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24-60</td>
<td></td>
<td>+/-</td>
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<tr>
<td></td>
<td></td>
<td>24-60</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>O, S, IM</td>
<td>5-30</td>
<td>10-40</td>
<td>2-5-20</td>
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<tr>
<td></td>
<td></td>
<td>10-30</td>
<td></td>
<td>+/–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-30</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>O, S, IM</td>
<td>2-5-15</td>
<td>5-20</td>
<td>2-5-10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-15</td>
<td></td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-15</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>Depot IM</td>
<td>Not for acute use</td>
<td>5-75 mg/2 wks</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>–</td>
</tr>
</tbody>
</table>

**(B) Other Typical Agents**

<table>
<thead>
<tr>
<th>NON-PROPRIETARY NAME</th>
<th>DOSAGE FORMS</th>
<th>ACUTE PSYCHOSIS</th>
<th>MAINTENANCE</th>
<th>METABOLIC SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molindone</td>
<td>O, S</td>
<td>15-50</td>
<td>30-60</td>
<td>15-50</td>
</tr>
<tr>
<td></td>
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<td>30-60</td>
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<td>30-60</td>
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<td></td>
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<td>–</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Loxapine</td>
<td>O, S, IM</td>
<td>15-50</td>
<td>30-60</td>
<td>15-50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30-60</td>
<td></td>
<td>+</td>
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<tr>
<td></td>
<td></td>
<td>–</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>O, S, IM</td>
<td>2.5-10</td>
<td>5-20</td>
<td>2.5-10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-15</td>
<td></td>
<td>+/-</td>
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<tr>
<td></td>
<td></td>
<td>5-15</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Haloperidol decanoate</td>
<td>Depot IM</td>
<td>Not for acute use</td>
<td>100-300 mg/month</td>
<td>+/-</td>
</tr>
<tr>
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**ATYPICAL ANTIPSYCHOTIC AGENTS**

<table>
<thead>
<tr>
<th>NON-PROPRIETARY NAME</th>
<th>DOSAGE FORMS</th>
<th>ACUTE PSYCHOSIS</th>
<th>MAINTENANCE</th>
<th>METABOLIC SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>O, S, ODT, IM</td>
<td>10-20</td>
<td>15-30</td>
<td>10-20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15-30</td>
<td></td>
<td>15-30</td>
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<tr>
<td></td>
<td></td>
<td>+/-</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Asenapine</td>
<td>ODT</td>
<td>10</td>
<td>10-20</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+/-</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Clozapine</td>
<td>O, ODT</td>
<td>200-600</td>
<td>400-900</td>
<td>200-600</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300-900</td>
<td></td>
<td>+++</td>
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<tr>
<td></td>
<td></td>
<td>+++</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>O</td>
<td>12-24</td>
<td>8-16</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+/-</td>
<td></td>
<td>+/-</td>
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<tr>
<td></td>
<td></td>
<td>–</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>O, ODT, IM</td>
<td>7.5-20</td>
<td>10-30</td>
<td>7.5-15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15-30</td>
<td></td>
<td>+++</td>
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<tr>
<td></td>
<td></td>
<td>+++</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>O</td>
<td>6-9</td>
<td>6-12</td>
<td>3-9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-15</td>
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<tr>
<td></td>
<td></td>
<td>+/-</td>
<td></td>
<td>+/-</td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>Depot IM</td>
<td>See note on dosing</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>O</td>
<td>200-600</td>
<td>400-900</td>
<td>200-600</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300-900</td>
<td></td>
<td>+</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>O, S, ODT</td>
<td>2-4</td>
<td>3-6</td>
<td>2-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-8</td>
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<tr>
<td></td>
<td></td>
<td>+/-</td>
<td></td>
<td>+/-</td>
</tr>
<tr>
<td>Sertindole</td>
<td>O</td>
<td>4-16</td>
<td>12-20</td>
<td>12-20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-32</td>
<td></td>
<td>+/-</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Ziprasidone*</td>
<td>O, IM</td>
<td>120-160</td>
<td>120-200</td>
<td>80-160</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120-200</td>
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<td>120-200</td>
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<tr>
<td></td>
<td></td>
<td>+/-</td>
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<td>–</td>
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</tbody>
</table>

*[Table adapted from Brunton, Chabner BA and Knollmann BC, 2011]*

Due to orthostasis risk, dose titration of iloperidone is 1 mg bid on day 1, increasing to 2, 4, 6, 8, 10, and 12 mg bid on days 2, 3, 4, 5, 6, and 7 (as needed). Safety data exist for daily doses up to 16 mg bid.

Paliperidone palmitate dosing in acute schizophrenia, deltoid IM loading doses of 234 mg at day 1 and 156 mg at day 8 provide paliperidone levels equivalent to 6 mg oral paliperidone during the first week, and peaking on day 15 at a level comparable to 12 mg oral paliperidone. No oral antipsychotic needed in first week. Maintenance IM doses can be given in deltoid or gluteus every 4 weeks after day 8. Maintenance dose options 39, 78, 117, 156, or 234 mg every 4 weeks. Failure to give initiation doses (except for those switching from depot) will result in subtherapeutic levels for months.

Risperidone oral dose must be given with food (500 kcal) to facilitate absorption. Food increases the absorption of single doses of 20-, 40-, and 80-mg capsules by 48%, 87%, and 101%, respectively.

Risperidone, olanzapine, and clozapine are three atypical antipsychotic medications commonly used in the management of chronic schizophrenia. While they offer advantages with regard to clinical efficacy and side-effect profile, few studies have compared them in a naturalistic prospective observational manner.
week-long prospective naturalistic observational study, Strous RD et al (2006) compared risperidone (n=38), olanzapine (n=38) and clozapine (55) in one hundred thirty-one patients (76 M, 55 F) both inpatients and outpatients, with DSMI-V schizophrenia or schizoaffective disorder over 12 weeks including illness characteristics and adverse effects. All patients showed a significant decrease of Positive and Negative Syndrome Scale (PANSS)-positive scores. Decreases in tardive dyskinesia and impulsivity scores were noted with clozapine and olanzapine, respectively. No differences between the medications were noted on depression, anxiety, EPS, or overt aggression scores. Males showed a decreased sexual performance irrespective of the medication and those treated with risperidone and clozapine showed greater proportional reduction of overt aggression. Clozapine-treated patients showed significant increased weight, increased glucose levels, and lowered sexual performance. Risperidone patients tended to exhibit reduced cholesterol levels. Higher creatine kinase (CK) levels were noted in risperidone-treated patients. While cautious given the nature of the study design, results suggest differences in the response to various atypical antipsychotic medications regarding efficacy and side-effect susceptibility. (Strous RD et al, 2006)

2.16. Atypical (Second Generation) Antipsychotics – Looking Beyond Efficacy

The atypical antipsychotics are notorious for having doses established in clinical trials that are not optimal in (real-world) clinical practice. This may be due in part to the differences between clinical trial patients and clinical practice patients, as well as to other factors such as concomitant medications, compliance, and concomitant substance abuse, among others. Although head-to-head experience suggests that one agent differs from another in this class mostly according to tolerability differences, many clinicians have observed one patient responding to one atypical antipsychotic better than to another in terms of efficacy. However, it has been difficult to predict which patients will respond to which agents other than by trial and error. (Hu RJ, 2011)

A George Awad, in his Guest Editorial “Second-Generation Antipsychotics Looking Beyond Efficacy” in The Canadian Journal of Psychiatry, May 2004 states that - A few years ago, he was asked to write about “The Aim of Antipsychotic Medications. What Are They and Are They Being Achieved?” He always believed that the aims of therapy with antipsychotic medications in schizophrenia are basically similar to the aims of therapy with medications used to treat long-term medical conditions that may require life-long treatment. Obviously, efficacy and safety are the major prerequisites for approval of new medications. However, in a long-term illness like schizophrenia, which has significant impact on several aspects of behaviour and mental and emotional functioning, it is equally important to demonstrate the impact of new medications on such issues as subjective tolerability, compliance, and quality of life. The best medications have no value unless
they are taken. Enhanced tolerability can improve medication compliance, which contributes to less-frequent relapse and less use of health resources, as well as improved quality of life.

A few decades ago, research on such outcomes as subjective tolerability or quality of life was looked at as soft science—a view reflected in a certain publication bias and low priority in research funding. In addition, new medical technology such as neuroimaging and neurogenetics attracted much of the research interest, particularly among young researchers. As the late Dr Theodore Van Putten, an early pioneer of research in neuroleptic dysphoria, once lamented in his personal communication to A George Awad “Research in neuroleptic dysphoria and subjective responses to medications, compared with neuroimaging, is not sexy anymore”. Few researchers (like George Awad) who persisted in researching these areas have already moved such outcomes to the forefront.

Subjective tolerability, quality of life, and medication compliance behaviour are now all recognized as important outcomes in the long-term management of schizophrenia [Awad AG (2004a), Awad and Voruganti (1995), Awad and Voruganti (1999)].

2.16.1. Meeting Everyday Challenges : Antipsychotic Therapy in the Real World

Patients with schizophrenia and their physicians face a number of challenges, such as long-term control of symptoms, maintaining cognitive function and subjective well-being, and preventing relapse (Gorwood P., 2006). Despite significant advances in our understanding of the nature of the disease, schizophrenia remains one of the most challenging medical conditions of our times. It is characterized by high morbidity and mortality, and available treatments for schizophrenia are incompletely and variably effective and associated with a range of adverse effects. (Tandon R. et al., 2008)

Despite these impediments, however, the individualized provision of a comprehensive array of treatment, rehabilitative and social support services can effectively promote recovery of persons with schizophrenia. Antipsychotic treatment needs to be individually tailored to promote optimal recovery and this requires careful monitoring and ongoing joint decision-making by the clinician-patient team about choice of antipsychotic agent, dosing, continuation/switching, and augmentation. While existing antipsychotic treatments for schizophrenia are not completely satisfactory, they can substantially reduce disease burden and make a meaningful difference in the life of each individual patient (Tandon R et al, 2008)
2.16.2. Schizophrenia Outpatient Health Outcomes (SOHO) Fig.22 (Ref. Haro JM, 2007)

Functioning
- Social relations
- Marital relation
- Hostility

Clinical severity
- Positive
- Negative

Patient reported
- Quality of life
- Depressive symptoms

Depressive
Overall
Cognitive

Fig.23 (Ref.: Tandon R. et al, 2008)

Schizophrenia - Recovery Means Optimizing Individual Outcomes

Treatment and Other Services

Rehabilitation (Enhance adaptive skills)
- Social skills training

Supports (Environmental changes)
- Supported housing
- Supported employment

Costs and unintended adverse consequences
- Side effects
- Related health risks

Treatment (Reduce symptoms and prevent relapse)
- Antipsychotics and other medications
- Cognitive Behaviour Therapy

Reduce Disease Burden

Add Treatment Burden

Recovery

Health & Wellness
- Vocational and/or educational functioning
- Independent living
- Physical health
- Instrumental competence
- Social integration
- Quality of life
2.16.3. Effectiveness (vs. Efficacy) as an Outcome Measure

As schizophrenia is a chronic disorder, determinant of drug’s effectiveness is not mere efficacy (symptom relief). Staying on the drug is critical for controlling symptoms and preventing relapse in schizophrenia. (Lieberman JA et al, 2005). Hence the emphasis in evaluating drug treatment benefits is shifting from ‘efficacy’ to ‘effectiveness’. Efficacy is defined as the desirable effect of an intervention, whereas effectiveness is the extent to which a product works in the patients to whom it has been offered. This meaning is slightly different from ‘efficacy’, which can be measured in those who have actually been treated. ‘Efficacy’ relates to explanatory studies and ‘effectiveness’ to pragmatic (practical) studies. Therapeutic efficacy (effectiveness) is often studied using observational surveys of patients whose treatments were selected nonexperimentally. (Korb FA et al., 2004)

Randomized clinical trials (RCTs) have long been the cornerstone of drug development as well as the eventual drug registration and regulation process. RCTs have been considered the ‘gold standard’ for establishing safety and efficacy due to their strong internal validity. However, RCTs are usually conducted applying strict protocol and regulatory guidelines. By design, RCTs require select populations; are often short. For these reasons, RCTs have been criticized for lacking external validity. This restricted external validity of RCTs may present limitations when translating the findings of RCTs to the real clinical practice settings, as they have indirect applicability to the general population of patients with schizophrenia (Dossenbach M et al., 2004).

Clinical trials of antipsychotics in schizophrenia patients have included highly selected patient populations, not truly representative of the patients these drugs would be used for in ordinary practice. Increasingly large drop-out rates in RCTs, sometimes linked to specific methodologies, have called into question analyses which in one way or another must impute results for missing values, and jeopardized simple conclusions – for example that a single treatment is likely to be effective in treating the target condition. The highly selected
samples and rigid experimental designs of traditional randomized, controlled trials may restrict their ability to deliver all clinically relevant information. Contradictory results in studies from different sources of pharmaceutical sponsorship may also contribute to the inconclusiveness of the evidence. Such studies can demonstrate efficacy, but the magnitude of the benefit cannot be simply extrapolated to real life. While randomised, placebo-controlled trials and open-label extensions can provide valuable information about the long-term efficacy and tolerability of newer antipsychotic agents, they cannot address all the variables that may affect treatment outcome. This led to the concept of effectiveness into play. In recent years, several studies of the effectiveness of antipsychotics have been launched to address some of the limitations associated with traditional randomized controlled trials (RCTs) of efficacy. Effectiveness trials, also known as “naturalistic”, “real-life”, “pragmatic”, or “practical” trials, address how a treatment works under normal clinical circumstances as distinct from the somewhat artificial settings of the efficacy trials. Through pragmatic designs and more global outcome measures, these trials have been expected to supplement the base of evidence regarding effectiveness of antipsychotics. (Johnsen et al. 2010)

Effectiveness studies aim to include an unselected or less selected group of patients by using broad inclusion criteria and few reasons for exclusion. Simple trial methodology may be employed to keep drop-out rates low. Rather than measuring the effects of therapeutic interventions on fairly specific outcomes in psychopathology, effectiveness studies aspire to measure something more tangible. An effectiveness study may examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. (McDonagh MS et al, 2010)

In psychiatry, death is too rare an outcome to consider, but admission to hospital or drug discontinuation are regarded as clinically relevant outcomes. (Fleischhacker WW and Goodwin GM, 2009) Factors such as cognitive function, antipsychotic side effects, patients' attitudes to medication and subjective well being can all affect the results of treatment in real-life clinical practice. In addition, patients themselves may refuse to participate in placebo-controlled studies because of a fear of being under-treated. The use of pragmatic measures in treatment trials facilitate the translation of study results into relevant clinical interpretations (Haro J.M et al., 2006). Naturalistic studies are, therefore, an important means of providing additional data on the safety and effectiveness of antipsychotic agents in 'real-world' settings (Gorwood P., 2006). Observational studies are therefore designed to assess the relevance and credibility of clinical trial outcomes in real-life settings. In doing so, they supplement findings from both randomised controlled trials (RCT) and epidemiological studies by allowing us to observe patterns in robust, real-world safety and effectiveness data from a naturalistic setting (Karagianis J et al., 2009)
Observational studies thus examine natural variations in exposure to treatments and describe associated outcomes. The major criticism of observational studies is linked to potential allocation bias and risk adjustment. But recent studies conducted across multiple therapeutic areas comparing RCTs and observational study findings found no major differences among estimates of treatment effects. Although naturalistic observational studies may have several limitations, they could also provide new insights. Due to their nature, observational studies can be used to evaluate drug use in everyday clinical practice settings and avoid protocol-induced bias. This kind of study can provide clinicians with valuable information about the relationship between the patient, the illness and the drug, and in so doing can address the needs and concerns of both the patient and the clinician. Naturalistic studies do not however negate the need for conventional studies (RCTs) that are essential in order to establish the efficacy and safety of new chemical compounds. In conclusion, both RCTs and nonrandomized (observational) studies can provide complimentary evidence (Korb FA et al., 2004).

To some extent, practical (pragmatic) trials can be conceptualized as hybrids of efficacy and large simple trials. Practical trials provide independent evidence to inform decision makers 'about the everyday effectiveness of clinically relevant alternative interventions.' Practical trial researchers include a heterogeneous population of patients and collect data 'on a broad range of meaningful health outcomes at many types of practice settings intended to represent usual treatment.' The designers of practical trials make trade-offs between internal validity, external validity, the breadth of issues addressed, and the ability to detect small differences. (Stroup T S. and Gedde J. R., 2008)

Studies across the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Unfortunately, for many drugs, there are few or no effectiveness studies and many efficacy studies (McDonagh MS et al, 2010). Nevertheless, most reported advantages of atypical over conventional antipsychotics have been found in double-blind clinical trials with often highly selected patient samples. Therefore, the effectiveness of these antipsychotics should be assessed, among others, in more naturalistic observational trials (Kudla D et al., 2007).

Efficacy outcomes are intermediate measures of efficacy and include schizophrenia symptomatology (general and negative symptom response), and measures of cognition, depression, and aggression. Intermediate outcome measures, such as improvement on symptom scales, typically are useful in determining efficacy of a drug. But they are not the ultimate goal of treatment; long-term effectiveness outcomes are. In the chain of evidence, there is a presumed link between the intermediate efficacy measure and a long-term effectiveness outcome, but these links are not always proven. Thus efficacy measures, because they represent intermediate steps to an effectiveness outcome, are only useful when there is no evidence on the long-term...
health outcome. For example, an improvement on a scale assessing negative symptoms is thought to lead to improvements in social functioning (McDonagh MS et al, 2010).

Effectiveness outcomes are the long-term health outcomes that are most important to patients. The best evidence comes from effectiveness trials. However, several efficacy trials and observational studies also contribute to the body of evidence. Effectiveness outcomes in the ‘Drug Class Review, Atypical Antipsychotic Drugs, Final Report Update 3’ include suicide or suicidal behavior, quality of life, hospitalization or relapse, persistence on the prescribed drug, and social functioning (McDonagh MS et al, 2010).

2.16.4. Time to Treatment (Medication) Discontinuation as a Measure of Effectiveness in the Treatment of schizophrenia

Second-generation antipsychotic drugs were introduced over a decade ago. They were intended to be more efficacious than were previous drugs for treatment of schizophrenia, and less likely to induce motor side-effects. However, their clinical effectiveness compared with first generation antipsychotic drugs is still debated. Indeed, limited conclusions can be drawn from the studies that have been undertaken so far, since most used restrictive inclusion criteria. Moreover, treatment response has almost exclusively been defined by use of scales that measure the extent of psychopathology in most studies, efficacy has been measured, according to narrowly-defined criteria, but not effectiveness, which is a combination of efficacy and tolerability. Kahn R. S and others (2008) have suggested that studies that are not restrictive in the inclusion of patients, have long follow-up periods, and use outcome measures which are clinically meaningful, are urgently needed.

Since schizophrenia is a chronic condition, understanding the longer-term differences between antipsychotic treatments is critical both to the selection of appropriate therapy. There is no doubt that conducting long-term clinical trials in schizophrenia is complicated. Many patients with schizophrenia discontinue their antipsychotic medication for various reasons. Others are simply lost to follow-up. In addition, it is unethical to continue patients on treatment over the long-term if they are not responding to a sufficient level. (Davey P and Others, 2003)

Time to all-cause medication discontinuation has been recognized as an important global index of antipsychotic effectiveness. It is considered a composite proxy measure of treatment efficacy, safety, and tolerability. Time to treatment discontinuation is increasingly used as a primary outcome measure in antipsychotic effectiveness research. (Shajahan P et al., 2010) It is a clinically meaningful outcome measure that integrates patients’ and clinicians’ judgments of efficacy, safety, and tolerability into a global measure of

All-cause discontinuation is a composite measure of 4 components consisted of lack of pharmacological efficacy, drug tolerability, clinician decision, and patient decision. Based on Stroup and colleagues (2003), the original concept of the all-cause discontinuation was used to compare the effectiveness of antipsychotic drugs in schizophrenia patients, given that these patients stop or change medication frequently, and that it is hard to measure many individual factors which caused discontinuation of treatment. Despite some of the limitations, the concept of all-cause discontinuation is a meaningful clinical measurement which reflected both efficacy and side effects for both the clinician and patients. (Lim SW et al., 2012)

Longer time to discontinuation of antipsychotic medication for any cause has been shown to be associated with greater symptom improvements in the treatment of schizophrenia (Dunayevich E et al, 2007). Persistence refers to the duration of time a patient continues to take a prescribed drug. In the setting of a study, this may also be referred to as early discontinuation or withdrawal from treatment during the trial period and can be assessed as a rate or the time to discontinuation. Because the reasons for discontinuing the assigned drug treatment encompass inadequate efficacy as well as intolerable side effects, discontinuation is considered a good measure of overall effectiveness. Discontinuation rates are higher among patients with schizophrenia than is typical in other diseases, with rates of 50% or more being common. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study used this outcome as the primary measure of effectiveness. (McDonagh MS et al, 2010)

This global proxy measure of medication effectiveness was the primary outcome measure in the National Institute of Mental Health – CATIE project (Ascher-Svanum H et al., 2006a). Thus time to antipsychotic medication discontinuation has recently been acknowledged by CATIE study. However, to close the gap between experimental clinical research and routine practice, open-label, non-randomised (naturalistic, observational) studies are also required. Early observational designs involving second-generation antipsychotics did not focus on treatment maintenance and the factors influencing it in everyday care. In contrast, the study by Ascher-Svanum et al. was specifically designed to evaluate time to antipsychotic discontinuation under routine clinical practice. (Ciudad A et al., 2008)

2.16.5. Time to Discontinuation in various Schizophrenia Studies where Atypical Antipsychotics were used:
In CATIE Phase 1, time to discontinuation for any reason was significantly longer with olanzapine than risperidone (hazard ratio 0.75, 95% CI 0.62-0.90), with a mean of 4.4 months longer, or quetiapine (hazard ratio 0.63, 95% CI 0.52, 0.76), with a mean of 4.6 months longer. Although differences among risperidone, quetiapine, and ziprasidone were found to be statistically significant, the clinical significance is limited, as the
Kaplan-Meir analysis of time to discontinuation for the 3 drugs was 4.4, 4.6, and 3.5 months, respectively. Olanzapine was also found to have a significantly longer duration of successful treatment (hazard ratio 0.69, \( P=0.002 \)) than risperidone. Time to discontinuation due to lack of efficacy was statistically significantly longer for olanzapine compared with quetiapine, hazard ratio 0.41 (0.29–0.57), risperidone, hazard ratio 0.45 (0.32–0.64) or ziprasidone, hazard ratio 0.59 (0.37–0.93). Differences between immediate release quetiapine, risperidone and ziprasidone were not statistically significant. In Phase 1B, time to discontinuation was statistically significantly longer with quetiapine (median 9.9 months, \( P=0.04 \)) and olanzapine (median 7.1 months, \( P=0.02 \)) than with risperidone (median 3.6 months). Time to discontinuation was longer with clozapine (10.5 months) than olanzapine (2.7 months, \( P=0.12 \)), quetiapine (3.3 months, \( P=0.01 \)), or risperidone (2.8 months, \( P<0.02 \)) in Phase 2E. Statistically significant differences were not found between the other atypical antipsychotics, although the small sample size may have resulted in inadequate power to find differences where they may exist. Further analysis of the time to discontinuation due to lack of efficacy indicated that clozapine was superior to all 3 of the other drugs. Time to discontinuation in Phase 2T was statistically significantly longer with risperidone (7 months) and olanzapine (6.3 months) than with quetiapine (4 months) or ziprasidone (2.8 months), but no difference was found between risperidone and olanzapine (hazard ratio 1.02, 95% CI 0.67–1.55). Further analysis of data from Phase 1 indicates that olanzapine and risperidone had significantly longer time to discontinuation due to lack of efficacy than quetiapine did. Olanzapine was also statistically superior to ziprasidone for this outcome (McDonagh MS et al, 2010).

Twelve retrospective observational studies also reported time to discontinuation with comparisons of atypical antipsychotics. The mean time to discontinuation with olanzapine compared with risperidone was significantly longer with olanzapine in 7 studies (mean of 251 days to discontinuation for olanzapine and 173 days for risperidone), while differences were not found in 3 studies (mean of 235 days to discontinuation for olanzapine and 228 for risperidone). Pooling of these results indicated a statistically significant difference of up to 66 days (95% CI, 59 to 73) longer with olanzapine. Comparisons of aripiprazole, olanzapine, or risperidone with immediate-release quetiapine had mixed results with no consistent finding of a superiority or inferiority. Comparisons of ziprasidone with olanzapine or risperidone did not find statistically significant differences in the time to discontinuation. (McDonagh MS et al, 2010)
2.16.6. Social functioning, Quality of Life and Subjective Tolerability as Measures of Effectiveness in the Treatment of Schizophrenia

Not long after the introduction of the first antipsychotic, chlorpromazine, many patients complained of an altered subjective state that could occur following even a few doses of the medication. Patients complained about feeling, “fuzzy or dull,” of being “unable to think straight,” and of feeling “like a zombie.” Some patients even believed that the medication made their conditions worse. Not surprisingly, many patients pressured their clinicians for frequent changes of medication, and some discontinued medication altogether. Despite these serious complaints, it took some time for clinicians and researchers to recognize the phenomena, which eventually were collectively labelled neuroleptic dysphoria. As clinical and research interest eventually focused on this issue, the consequences of neuroleptic dysphoria and lack of subjective tolerability were increasingly recognized. Their negative impact on adherence behaviour and on eventual outcome includes frequent relapses, excessive utilization of resources, hospitalizations, and compromised quality of life. (Awad AG & Voruganti LNP, 2004)

Recent neuroimaging techniques have allowed to test such hypotheses in a recent single photon emission computed tomography dopamine depletion study. In it, Awad and Voruganti were able to induce dysphoria in a sample of medication-free patients with the diagnosis of schizophrenia. They demonstrated a significant correlation between dysphoric responses and dopamine binding ratio in the striatal-accumbens complex. This study had another important finding: the demonstration of variability in basal dopamine activities, which probably explains why not every patient receiving antipsychotics develops dysphoria. Patients who have relatively lower dopamine activities are likely to develop dysphoria when given a potent D2 receptor antagonist. This in turn can explain, at least in part, why patients taking second-generation antipsychotics develop less dysphoria and are able to subjectively tolerate the medications better, since their impact on the dopamine receptor is much less pronounced or transient in nature. These data have received confirmation from a series of PET studies comparing dopamine receptor occupancy in patients receiving either first- or second-generation antipsychotics. Despite such recent breakthroughs in understanding the neurobiology of neuroleptic dysphoria, only limited clinical data indicate a strong trend toward more positive attitudes toward medication and a more favourable impact of second-generation antipsychotics on subjective tolerability. (Awad AG & Voruganti LNP, 2004)

Thus over the last few years, the concept of quality of life has become a new paradigm for representing the ideal of modern medicine emphasizing biopsychosocial approaches. In other words, the concept has come to represent the ultimate outcome of the interaction between the patient and the illness, its treatment, its psychosocial impact, and its consequences. In that context applied to schizophrenia, the impact of
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Antipsychotics is considerable, not only because of their ability to alleviate symptoms but also because of the impact of side effects on how patients feel and function. The challenging question is not only to document improved quality of life with second-generation antipsychotics but also to demonstrate that this improved quality of life can translate into better functional states, less utilization of resources, and greater overall satisfaction. Since second-generation antipsychotics lack many of the side effects, particularly the extrapyramidal side effects, of the first-generation antipsychotics, they can be expected to be subjectively better tolerated. Again, however, a survey of the literature indicates that few studies have explored the impact of second-generation antipsychotics on subjective tolerability and attitudes of patients toward medications. (Awad AG & Voruganti LNP, 2004)

Recent research has shown that atypical antipsychotics improve QOL in patients with schizophrenia. However, studies that incorporate QOL in the assessment of long-term effectiveness are limited and inconsistent. When measuring QOL in patients taking antipsychotics, it is important to acknowledge that a variety of factors may influence QOL outcomes. These include side effects and daily dosage of the antipsychotic, depressive and negative symptoms, duration of treatment, and subjective tolerability. (Kwon JS et al., 2009)

In a double-blind, randomized controlled trial, Rosenheck et al. (2003) reported that measures of effectiveness demonstrated no advantage for olanzapine compared with haloperidol in overall QOL. In contrast, a naturalistic observational study by Endicott J et al. (1993) on patients with schizophrenia undergoing usual care indicated that ziprasidone treatment resulted in improved satisfaction with general activity as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire.

A large noncomparative postmarketing study of schizophrenia patients treated with risperidone reported significant improvement in quality of life (58% of patients) by week 10, compared with only 25% at baseline. In another long-term study, 362 schizophrenia patients were switched from other antipsychotics to risperidone. Improvement in quality of life was reported following 8 months of treatment. Several studies comparing the impact of risperidone and olanzapine on quality of life indicated similar improvement in both groups. Several studies reported the superiority of clozapine to first-generation antipsychotics in improving quality of life for treatment-refractory schizophrenia patients (Awad AG & Voruganti LNP, 2004). Other comparative studies concluded that patients taking olanzapine demonstrated more improvement in quality of life, compared with those taking haloperidol.
2.16.7. The Impact of Subjective Well-being Under Neuroleptic treatment (SWN) on Compliance and Remission (de Millas W and others, 2006)

The patients' perspective of antipsychotic treatment was largely neglected for a long period. It has only been during the last 10 years, with the development of atypical antipsychotics, treatment goals became more ambitious, the patient's perspective was considered more, and complaints such as affective blunting and cognitive slowing, as well as volition and loss of spontaneity, received greater interest. These emotional restrictions have been described as “neuroleptic dysphoria,” “pharmacogenetic depression,” “akinetic depression,” “neuroleptic depression,” and “neuroleptic-induced anhedonia.”

Despite significant advances in the pharmacotherapy of schizophrenia, noncompliance, particularly in long-term treatment, remains a major problem. Although compliance somewhat improved under treatment with atypical antipsychotics, adherence rates at 6 and 12 months were only moderately higher compared with patients receiving typical agents. Since noncompliance is one of the most important risk factors for relapse, enhanced medication adherence is an urgent task. Due to the advances in psychopharmacological as well as psychosocial/psychoeducational treatments, chances for better long-term prognosis have been improved, and remission has become a major goal in the treatment of schizophrenia.

Subjective well-being (SW) is a major component of quality of life influenced by the pharmacological and/or psychosocial treatment as well as by the illness itself. The impact of antipsychotic drugs on subjective wellbeing, together with the quality of the doctor-patient relationship, is one of the two agreed major determinants for medication compliance.

The effects of antipsychotic treatment on psychopathology and on subjective well-being (SW) are not strongly related; the perspectives of the patient and his/her psychiatrist markedly differ. Recent research indicates that SW/quality of life, much more improved by atypical than by typical antipsychotics, has a strong impact on compliance, as well as on the chance of achieving remission. The data strongly suggest that a systematic evaluation of the patient's perspective of antipsychotic treatment is meaningful and necessary to increase compliance, functional outcome, and long-term prognosis.

2.16.8. The Relationship Between Psychopathology And Subjective Well-Being & Measurement of Subjective Well-being (de Millas W and others, 2006)

For a long period, many psychiatrists believed that they knew their patients well enough not to need additional self-ratings by the patients. However, numerous trials have revealed that both perspectives differ markedly regarding the relevance of side effects or success of antipsychotic treatment. Subjective well-being is at least a valuable addition to objective psychopathology, and should become an integral part of shared
decision-making A better consideration of the patients' perspective can improve therapeutic alliance, medication adherence, and finally, the long-term prognosis.

Studies on subjective well-being (SW) disproved the former belief that schizophrenic patients are not able to reliably assess their SW. The majority of schizophrenic patients, if not acutely psychotic or suffering from severe cognitive impairment, are able to complete self-rating scales in a consistent and reliable manner.


2.16.9. Studies related to Subjective Well-Being under Neuroleptic Treatment (SWN) and Overall Functioning in Schizophrenia:

The relationship between psychopathology, as shown with the Positive and Negative Syndrome Scale (PANSS), and the subjective well-being under neuroleptic treatment (SWN), was investigated in several trials. The total score, as well as the subscales were only moderately correlated with the PANSS scores ($r=-0.1$ to $-0.5$) with stronger relationships to the negative and global score than to the positive score. The highest correlations ($r=-0.4$ to $-0.5$) were related to the severity of depression and anxiety. Regarding the impact of side effects, Lambert M et al (2004) found, in a study in 213 patients treated with typical neuroleptics, that sexual dysfunctions and extrapyramidal and psychic side effects were rated as subjectively more distressing than vegetative side effects and sedation (de Millas W and others, 2006).

In a study by de Haan et al. (2000) it was shown that dosage of medication leading to dopamine ($D_2$) receptor blockade should be carefully evaluated, since it is most likely responsible for neuroleptic dysphoria, even in the absence of motor side effects (Voruganti LP and Awad AG, 2005 and Bressan RA, Crippa JA., 2005). The relationship between SWN and striatal $D_2$ receptor occupancy was investigated in 22 schizophrenic patients, clinically stable under either 14.7 mg of olanzapine or 4.1 mg of risperidone. It was demonstrated that in the absence of extrapyramidal symptoms, higher striatal $D_2$-receptor occupancy as measured by single photon-emission computed tomography (SPECT) was related to reduced SWN, negative symptoms, and depression ($P<0.01$) (de Millas W and others, 2006).
In an first ever study by Mirzahi et al (2009) to investigate subjective well-being with partial agonist (aripiprazole) and its association with dopamine D2 receptor binding potentials and occupancy, subjective well-being was measured using the SWN (subjective well-being under neuroleptic treatment) scale and was related to dopamine D2 receptor occupancy using [11C]raclopride PET. Patients that were switched to aripiprazole showed improvement in their subjective well-being from 79.80 (SD 16.08) to 89.90 (SD 15.33), an effect that was sustained for 6 months. This sustained improvement was observed despite very high levels of dopamine D2 receptors occupancy (82–99%), in contrast to the effects of antagonist antipsychotics on subjective well-being. The authors reported a) putative early and sustained improvement in subjective well-being in patients switched to aripiprazole, b) in contrast to antagonist antipsychotics (de Haan et al. 2000) aripiprazole did not induce dysphoric effects even at very high levels of dopamine D2 occupancy; c) while the antagonist antipsychotics showed an inverse relationship between occupancy and SWN Scale, aripiprazole did not.

In a randomized control trial by Naber et al (2005) olanzapine (n=57) and clozapine (n=57) were compared in a double-blind, controlled trial in 114 patients, over a 26-week period. Regarding SWN, the total score—as well as all subscores, excluding mental functioning—showed a significant relationship between low SWN and noncompliance (P<0.005 – P<0.01). Again, this study showed that the improvement of SWN and of PANSS are not strongly related with a correlation coefficient of r= -0.45 indicating that patients and psychiatrists perceive treatment differently.

In SOHO (Schizophrenia Outpatient Health Outcomes) study, [conducted in 10 Western European countries, (Garavan J et al, 1998 and Marder SR, 1998) and in 27 countries across 4 continents as the Intercontinental SOHO (IC-SOHO) (Liddle PF and Barnes TRE., 1988), which was a 3-year, prospective, observational study primarily designed to assess the comparative costs and outcomes associated with antipsychotic use in outpatients initiating or changing antipsychotic medication for schizophrenia (with an emphasis on olanzapine compared with other antipsychotics)] also found a relevant relationship between subjective well-being and compliance. In the SOHO study, SWN scale was used as an important single component of the complete remission criterion (de Millas and others, 2006).

A multicenter, open-label, prospective clinical study was conducted for 12-week observation period in 480 inpatient and outpatient schizophrenic population to assess the effect of paliperidone ER (with flexible dosing in the range 3-12 mg/day) on symptoms and functioning. Treatment of these subjects was decided by clinicians’ opinion. In the present study significant improvements in patients’ personal and social functioning with paliperidone ER treatment were observed (Huang MW et al, 2012).
Among Indian studies, Padmavati et al (1995) developed the SCARF Social Functioning Index to measure social functioning and assessed the reliability and validity of the instrument. Thara et al (1998) devised the Burden Assessment Schedule (BAS) to assess the subjective and objective burden on caregivers of mentally ill patients. In 100 patients with their primary caregivers attending a Psychiatry OPD, Creado, Parkar and Kamath (2006) assessed the level of functioning of the patient with Global Assessment of Functioning (GAF) Scale with the aim to evaluate the burden and coping of caregivers in relation to the level of functioning in patients with chronic schizophrenia measured by Burden Assessment Schedule (BAS) and Mechanisms of Coping (MOC) scale. The use of problem-solving coping by caregivers showed a significant correlation with higher level of (improvement in) functioning in patients (cited by Kulhara P et al, 2010).

Although the ability to maintain social relationships is a key goal for patients with schizophrenia, few studies have assessed social function as a specific and primary outcome measure. Social function outcomes that are objective and measured directly, such as employment status, are preferred to indirect or proxy measures by scales like the Social Function Scale (SFS), which is generally patient self-assessment of social ability. In a 12-month effectiveness trial (N=108), no significant differences were seen between olanzapine and risperidone based on the Role Functioning Scale (RFS) or the Social Adjustment Scale (SAS) – Severely Mentally Ill version (Jerrell JM, 2002). In contrast, in a 1-year open-label trial (N=235), improvement on the SFS was greater with olanzapine (+7.75) than risperidone (-0.92; P=0.0028)(Ciudad A and others, 2006). Differences on subscale items were found for occupation or employment, recreation, independence (performance), and social engagement or withdrawal. Using the Psychiatric Status You Currently Have (PSYCH) tool, a small, 6-month study (N=42) compared olanzapine and risperidone and did not find statistically significant differences on financial dependence, impairment in performance of household duties, relationship impairments (family and friends), or recreational activities. Those on olanzapine had improvement on occupational impairment scores while those on risperidone had decreased scores, but the difference did not reach statistical significance (Ho BC and others, 1999). A very small 10-week trial (N=19) of patients with a history of resistance to prior antipsychotic treatment randomized patients to clozapine or risperidone, but did not find differences between the drugs based on the GAF scale or the SFS (Wahlbeck K and others, 2000a).

2.17. Effectiveness of Atypical Antipsychotics (with focus to Risperidone, Olanzapine and Clozapine)

The past decade witnessed major changes in the practice of antipsychotic therapy around the world. The sequential introduction of eleven “atypical” or second generation antipsychotics (clozapine, amisulpride, zotepine, risperidone, olanzapine, quetiapine, sertindole, ziprasidone, aripiprazole, perospirone, and paliperidone), led to increased optimism among physicians and patients about what can be achieved with effective antipsychotic therapy in schizophrenia. (Tandon R. et al., 2008)
SGAs were considered by practitioners to be more effective than FGAs in terms of possessing a broader spectrum of efficacy (particularly with regard to negative, cognitive, and mood symptoms) and having a lower liability to cause acute and long-term motor side-effects. Even as many experts believed that SGAs are substantially better than FGAs, some questioned any such advantage. Governments and clinicians also became increasingly skeptical about available comparative information about antipsychotic agents, much of which was derived from pharmaceutical industry-sponsored trials (Melander et al., 2003; Perlis et al., 2005; Lexchin et al., 2003; Montgomery et al., 2004; Heres et al., 2006). It was consequently hoped that results of two large government-sponsored studies [Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) in schizophrenia in the U.S. (Lieberman et al., 2005; McEvoy et al., 2006; Stroup et al., 2006a) and Cost Utility of the Latest Antipsychotics in Severe Schizophrenia (CUtLASS) in the U.K. (Lewis et al., 2006a&b, Jones et al., 2006)] would provide definitive answers. (Tandon R. et al., 2008)

a) Risperidone versus Other Atypical Antipsychotics

In one of the most important and cited multicenter double-blind CATIE study on the effectiveness of antipsychotic drugs (Lieberman JA et al., 2005), risperidone confirmed to be a highly effective antipsychotic treatment with an excellent safety/effectiveness index ratio. 1493 patients with schizophrenia randomly assigned to receive olanzapine (mean modal daily dose 20.1 mg), perphenazine (mean modal daily dose 20.8 mg), quetiapine (mean modal daily dose 543.4 mg), or risperidone (mean modal daily dose 3.9 mg), ziprasidone (mean modal daily dose 112.8 mg), were assessed for up to 18 months for the overall effectiveness of these five treatments. Seventy-four percent of patients discontinued the study medication before 18 months. The time to the discontinuation of treatment for any cause was significantly longer in the olanzapine group than in the quetiapine (P < 0.001) or risperidone (P = 0.002) group, but not in the perphenazine (P = 0.021) or ziprasidone (P = 0.028) group. The times to discontinuation because of side effects were similar among the groups, but the rates differed (P = 0.04); olanzapine was associated with more discontinuation for weight gain or metabolic effects, and perphenazine was associated with more discontinuation for EPS. As in all head to head comparison studies of second generation antipsychotics (SGA), a key problem is the employed dose. In the CATIE study, the use of a higher-than-usual peak dose of olanzapine may have led to the superior results achieved with it. Regarding risperidone, its relatively less than optimal effectiveness in comparison with olanzapine and its favorable side effects profile is probably due to the low mean modal daily dose of this drug used in the study. (Raja Michele, 2009)

In the phase 2 of the CATIE study, 8 subjects with schizophrenia (N = 444) who had discontinued the atypical antipsychotic randomly assigned during phase 1 of the CATIE investigation were randomly reassigned to double-blind treatment with a different antipsychotic (olanzapine, 7.5–30 mg/day [N = 66]; quetiapine, 200–800 mg/day [N = 63], risperidone, 1.5–6.0 mg/day [N = 69]; or ziprasidone, 40–160 mg/day [N = 135]). The
time to treatment discontinuation was longer for patients treated with risperidone (median 7.0 months) and olanzapine (6.3 months) than with quetiapine (4.0 months) and ziprasidone (2.8 months). Among patients who discontinued their previous antipsychotic because of inefficacy (N = 184), olanzapine was more effective than quetiapine and ziprasidone, and risperidone was more effective than quetiapine. There were no significant differences between antipsychotics among those who discontinued their previous treatment because of intolerability (N = 168). Consistent results were reported in the study of Mullins et al. (2008). These authors assessed discontinuation at one-year follow-up in a population of patients with schizophrenia initially treated with aripiprazole (n = 446), olanzapine (n = 1705), quetiapine (n = 1467), risperidone (n = 1580), and ziprasidone (n = 700). Most patients discontinued their antipsychotic medication (90.4% adjusted mean discontinuation). The hazard ratio (HR) for discontinuing therapy in patients starting treatment on aripiprazole, risperidone, or ziprasidone was not significantly different from olanzapine [HR 1.047, 0.973 and 0.990, respectively]. Quetiapine was associated with significantly higher hazard of discontinuation [HR 1.130] than olanzapine (Raja Michele, 2009).

In most head to head comparison studies with other antipsychotics, risperidone showed a clinical efficacy similar to that of other compounds in the treatment of acute psychosis [comparison with olanzapine], acute and chronic schizophrenia [comparison with quetiapine], acute psychosis in the emergency setting [comparison with olanzapine and quetiapine], early psychosis [comparison with olanzapine and quetiapine], acute first-episode nonaffective psychosis [comparison with haloperidol and olanzapine], resistant or intolerant schizophrenia [comparison with olanzapine], chronic schizophrenia or schizoaffective disorder [comparison with ziprasidone], schizophrenia-spectrum disorders in children and adolescents [comparison with olanzapine and quetiapine], first-episode schizophrenia [comparison with haloperidol]. (Raja Michele, 2009)

A randomized open-label trial (McCue RE et al., 2006) for a minimum of 3 weeks in acutely ill patients with schizophrenia, schizoaffective disorder or schizoaffective disorder found that haloperidol (89%), olanzapine (92%) and risperidone (88%) were significantly more effective than aripiprazole (64%), quetiapine (64%) and ziprasidone (64%) in improving mental status so that the patients no longer required acute inpatient care. Changes in BPRS (Brief Psychotic Rating Scale) ratings were not significant among treatments, however.

In a double-blind, randomized, controlled flexible-dose trial (Schooler N et al., 2005), that compared risperidone (mean modal dose = 3.3 mg) and haloperidol (mean modal dose = 2.9 mg), first-episode psychosis patients (N = 555, mean age = 25.4 years) treated with both treatments achieved initial clinical improvement, defined as > 20% reduction in total PANSS score. However, among those who achieved clinical improvement, 42% of the risperidone group experienced a relapse compared with 55% of the haloperidol.
group. The median time to relapse was 466 days for risperidone-treated subjects and 205 days for those given haloperidol.

In the Intercontinental Schizophrenia Outpatient Health Outcomes (Bitter I et al, 2005) non-interventional, prospective observational study, olanzapine and risperidone were superior to haloperidol and clozapine in reducing aggression in psychotic patients. In a naturalistic study (Raja M and Azzoni A, 2003), the effectiveness and safety of quetiapine, risperidone and olanzapine were compared in the treatment of nonselected acutely psychotic patients admitted to a psychiatric intensive care unit. It was observed that the rate of antipsychotic switch because of a lack of efficacy or side effects was higher in the quetiapine treated cases in comparison with the risperidone or olanzapine treated cases. The proportion of cases concomitantly treated with typical neuroleptics was significantly higher in the quetiapine group compared with the other two groups. In the outcome of non-crossover cases, there were more improvements in the risperidone and olanzapine groups than in the quetiapine group. In a study by McEvoy JP et al. (2006) comparing switching to clozapine with switching to olanzapine, quetiapine, or risperidone in patients with resistant schizophrenia who had discontinued treatment with a newer atypical antipsychotic in the context of the CATIE investigation found clozapine was more effective than switching to another newer atypical antipsychotic.

In the Intercontinental Schizophrenia Outpatient Health Outcomes (SOHO) naturalistic, prospective observational study on outpatients with chronic schizophrenia, (Dossenbach M et al, 2004) at 6 months, olanzapine resulted in significantly greater improvements in overall, positive, negative, depressive, and cognitive symptoms compared with quetiapine, risperidone or haloperidol (p < 0.001). Improvements in overall, negative, and cognitive symptoms were significantly higher for risperidone compared with haloperidol (p < 0.001), whereas improvements across all symptoms were comparable for quetiapine and haloperidol. Many randomized controlled trials, naturalistic studies and extensive clinical experience have definitively shown clear efficacy and effectiveness of risperidone in the treatment of schizophrenia, schizoaffective disorders and other schizophrenia spectrum disorders, as well as of other psychotic disorders.

On the basis of available evidence, no other antipsychotic drug (neither of first nor of second generation) has shown superior clinical effectiveness in the treatment of psychotic disorders, with the significant exception of clozapine. Even at high dose, risperidone is characterized by a profile of motor side effects much more favorable in comparison with FGA. Currently, FGA should not be considered first line treatment of psychotic disorders. In comparison with SGA, risperidone is characterized by a very potent antagonist action on postsynaptic dopaminergic receptors, roughly similar to that of olanzapine, amisulpride, and sertindole, which accounts for its high efficacy and effectiveness on positive psychotic symptoms. (Raja Michele, 2009)
Other SGA, including quetiapine, aripiprazole, ziprasidone show a somewhat inferior efficacy on positive psychotic symptoms probably due to a less strong antagonist action on post-synaptic dopaminergic receptors. With the possible exception of clozapine, there are no data pointing to a difference in efficacy on so-called negative (primary or secondary) symptoms among SGA. Furthermore, there are some other features of risperidone that render it uniquely useful in the management of psychotic disorders, currently. (Raja Michele, 2009)

Risperidone is the unique choice among SGA for patients with psychotic symptoms, who need antipsychotic treatment at very high daily dosage, (Raja Michele, 2009) including:

1. patients with severe positive psychotic symptoms, hostility, aggressiveness and violent behavior;
2. patients with high drug metabolism due to enzymatic induction caused by smoking, alcohol or drug (e.g. carbamazepine) or due to genetic factors,
3. patients long-term treated with high dosage of anti-dopaminergic drugs, especially FGA, who present a supersensitivity of their post-synaptic dopaminergic receptors and show a severe relapse of positive psychotic symptoms whenever the antagonistic post-synaptic dopaminergic action lessens.

Among the SGA, risperidone is probably the drug best suited to substitute haloperidol in the clinical practice, in all settings. However, risperidone presents major limitations both on the level of efficacy and of side effects. A substantial number of patients with psychotic symptoms do not respond to risperidone, whatever its dose. Most of these patients are unlikely to respond to other FGA or SGA (although trials are worthwhile) and will need clozapine. For a minority of risperidone treated patients, EPS and TD remain a serious concern. HPRL (hyperprolactinemia) related side effects may be severe, unacceptable and even dangerous in some patients. (Raja Michele, 2009)

b) Olanzapine versus Other Atypical Antipsychotics

Johnsen E and Jørgensen HA (2008) located sixteen different reports of randomized head-to-head comparisons of SGA effectiveness. In acute-phase and first-episode patients, no differences between the SGAs were disclosed regarding alleviating disease symptoms. Olanzapine was associated with more weight gain and adverse effects on serum lipids. In the chronic phase, patients olanzapine groups had longer time to discontinuation of treatment and better treatment adherence compared to other SGAs. The majority of studies found no differences between the SGAs in alleviating symptoms of psychosis in chronically ill patients. Olanzapine was associated with more metabolic adverse effects compared to the others SGAs. There were surprisingly few between-drug differences regarding side effects. First generation antipsychotics were associated with lower total mental health care costs in 2 of 3 studies on chronically ill patients, but were also associated with more extrapyramidal side effects compared to the SGAs in several studies. There were differences regarding sample sizes, inclusion criteria and follow-up periods, as well as sources of...
financial sponsorship. Despite limitations mentioned, it was concluded by the Johnsen E and Jørgensen HA that in chronically ill patients olanzapine may have an advantage over other SGAs regarding longer time to treatment discontinuation and better drug adherence, but the drug is also associated with more metabolic side effects. Authors also feel that more effectiveness studies on first-episode psychosis are needed. (Johnsen E and Jørgensen HA, 2008)

In a Drug Effectiveness Review Project report of Atypical Antipsychotics by McDonagh MS et al, 2010, the risk of relapse appeared to be lower with olanzapine than quetiapine over 1 and 3 years of follow up. Results favored olanzapine over risperidone in a 28 week trial and a 3 year observational study but differences were not found in another observational study with 1 year of follow up. Good-quality trial evidence indicated lower risk of hospitalization with olanzapine compared to quetiapine, risperidone, and ziprasidone. Observational study results were conflicting. In case of quality-of-life measures, good-quality trial evidence did not differentiate olanzapine, quetiapine, risperidone, or ziprasidone, although improvements were seen with all the drugs. In case of social functioning, differences were not found between olanzapine, quetiapine, risperidone, and ziprasidone, although olanzapine might improve function better than ziprasidone in those with depressive symptoms, and compared with quetiapine in those with predominantly negative symptoms. As regarding rate and time to discontinuation of drug, olanzapine had lower discontinuation rates than aripiprazole, asenapine, iloperidone, quetiapine, risperidone, and ziprasidone, based on mixed-treatment comparison analysis of multiple trials, controlling for within-study dose comparisons and duration of study. Based on the CATIE trial Phase 1, olanzapine was also found to have longer time to discontinuation than quetiapine, risperidone, and ziprasidone. While limited evidence indicated that clozapine may be superior to olanzapine. Under trial circumstances, the difference was approximately 4 months longer with olanzapine, while observational studies indicated a much smaller difference, around 46 to 66 days longer. (McDonagh MS et al, 2010)

In a prospective, comparative, nonrandomized, open-label, multisite, observational study of Spanish inpatients with an acute episode of schizophrenia that assessed the effectiveness and safety profile of olanzapine in comparison with other antipsychotics, patients treated with olanzapine in monotherapy (OGm) and 385 patients treated with conventional antipsychotics (CG) were included in the analysis. Treatment-emergent EPS were significantly higher in the CG (p <0.0001). Response rate was significantly higher in the OGM (p =0.005). Logistic regression analyses revealed that the only variable significantly correlated with treatment-emergent EPS and clinical response was treatment strategy, with patients in OGM having 1.5 times the probability of obtaining a clinical response and patients in CG having 5 times the risk of developing EPS. In this naturalistic observational study it was concluded that olanzapine in monotherapy was better-tolerated and at least as effective as conventional antipsychotics. (Ciudad A et al, 2005)
c) Clozapine versus Other Atypical Antipsychotics

In band 2 of CUtLASS study (Lewis et al., 2006b), 136 patients exhibiting a poor response to ≥ 2 antipsychotic agents were randomized to receive either clozapine or a non-clozapine SGA and their quality of life compared over one year. Clozapine was found to be significantly superior to non-clozapine SGAs with reference to symptoms (p=0.01) and exhibited a trend towards superiority with regard to quality of life (p=0.08) in this group of patients. In fact, among patients with treatment refractory schizophrenia, clozapine still has the largest body of evidence supporting its greater efficacy (Kane et al., 1988, Chakos et al., 2001; Tuunainen et al., 2002), its potential for agranulocytosis and other major adverse effects has generally limited its use to patients with otherwise treatment-refractory schizophrenia. Results from the efficacy arm of phase-2 in CATIE (McEvoy et al., 2006) also support the greater efficacy of clozapine in poorly responsive schizophrenia patients. In contrast to the compelling data supporting its superiority over FGAs and other SGAs in treatment-refractory patients and those with high suicidality (Meltzer et al., 2003), there is no such evidence of clozapine's greater effectiveness in first-episode (Lieberman et al., 2003) or other patient populations (Tandon R et al., 2008).

2.18. Atypical Antipsychotics - Response Rates in the Treatment of Schizophrenia

Response rates across the atypical antipsychotics range widely across trials, due to variations in patient populations, duration of follow-up, and definition of response.

In a Drug Effectiveness Review Project report of Atypical Antipsychotics by McDonagh MS et al, 2010, across the reviewed trials, statistically significant differences in response rates were found very rare, with these differences occurring only when data were analyzed according to multiple definitions of response or when only patients completing a 12-month trial period were included. In these cases, however, other analyses or other trials have not confirmed findings of a difference. Four trials of comparing olanzapine with risperidone reported response rates. [Conley RR, Mahmoud R (2001), Gureje O et al (2003); Jeste DV et al (2003); Tran PV et al (1997)] Each of these trials reported response rates of >20% on the PANSS, but only the Gureje study found a statistically significant difference on this measure (olanzapine 75%, risperidone 47%, P=0.01). Pooled analysis resulted in no significant difference between two drugs in their response rates. Three trials by Conley, Gureje and Tran also reported response rates defined as >40% improvement on the PANSS. Tran found the difference was just statistically significant (P=0.049), favoring olanzapine, Gureje found no difference, and Conley found risperidone superior (P<0.03). Pooling these data does not result in a significant difference (P=1.07, 95% CI 0.59 to 1.93) Tran also found a significant difference favoring olanzapine among those with > 50% improvement on the PANSS.
Four studies comparing clozapine with risperidone reported response rate. Three defined response as a 20% improvement in the total PANSS score, and 1 used the Kane criteria. Using the Kane criteria, the Azorin study found 48% of the clozapine group improved, as did 43% of the risperidone group, $P<0.38$. Similarly, the pooled results of the 3 studies that used a 20% improvement definition does not indicate a significant difference between the drugs based on this criterion (McDonagh MS et al, 2010). Two trials comparing clozapine with olanzapine used the Kane response rate criteria as the primary measure but also reported response rates based on improvements on the PANSS. Bitter (2004) found no difference between the drugs, but Tollefson (2001) found significantly more patients classified as responding to olanzapine when using $\geq 30\%$ and $40\%$ on PANSS score as the criterion. However, pooling data from these 2 studies does not result in statistically significant differences based on any criteria. Risk Difference analysis also did not result in statistically significant differences. A small, exploratory, crossover trial comparing high-dose olanzapine (50 mg/d) with clozapine (450 mg/d) for 8 weeks each in treatment-resistant inpatients found that 10% met criteria for response ($20\%$ improvement in BPRS) while on clozapine, while none met the criteria on olanzapine (Conley RR, Mahmoud R., 2001).

An 8-week trial comparing immediate-release quetiapine with risperidone found no differences in response rates based on $\geq 30\%$ or $40\%$ improvement in the PANSS total score. Similarly, a 52-week trial of quetiapine, risperidone, and olanzapine also found no differences in response rates using a definition of $\leq 3$ on all PANSS items and $\leq 3$ on the CGI-S. Based on 3 trials comparing ziprasidone with olanzapine (N=269), risperidone (N=139), or clozapine (N=146), statistically significant differences in response rates were not found using a variety of measures. Based on 20%, 30%, and 40% improvement in total BPRS score, no differences were found between ziprasidone and olanzapine. In an 8-week trial comparing ziprasidone with risperidone, numerically more patients in the risperidone group were classified as responders based on 20%, 30%, and 40% improvement in the PANSS, while more patients in the ziprasidone group were classified as responders at the 50% improvement level, but the differences were not significant. Based on a study of aripiprazole and risperidone, no statistically significant differences in response rates found, defined as a $\geq 30\%$ decrease in PANSS or a score of 1 or 2 on the CGI-I scale (36% with aripiprazole 20 mg daily, 40% with aripiprazole 30 mg daily, and 41% with risperidone 6 mg, $P=0.49$ by our chi-square analysis). (McDonagh MS et al, 2010).
### Table 11: Olanzapine and Risperidone - Response rates: Mean change in PANSS >20% from baseline

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N, Duration</th>
<th>Response rate (%)</th>
<th>Olanzapine</th>
<th>Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conley, 2001</td>
<td>N = 377 8 weeks</td>
<td>45%</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Jeste, 2003</td>
<td>N = 175 8 weeks</td>
<td>58%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Tran, 1997</td>
<td>N = 339 28 weeks</td>
<td>61%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>Gurje, 2003</td>
<td>N = 62 30 weeks</td>
<td>75%</td>
<td>47%</td>
<td></td>
</tr>
</tbody>
</table>

**Pooled relative risk 1.04 (95% CI 0.89 to 1.21)**
Q = 4.96 (df = 3) P=0.17
**Pooled risk difference 0.03 (95% CI -0.07 to 0.11)**
Q = 5.87 (df = 3) P = 0.12

### Table 12: Clozapine and Olanzapine: Response rates for 3 definitions of response

<table>
<thead>
<tr>
<th>Author, Year, N</th>
<th>Kane criteria (% responders)</th>
<th>PANSS &gt;30% (% responders)</th>
<th>PANSS &gt;40% (% responders)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitter 2004, N = 140</td>
<td>Clozapine 61, Olanzapine 58</td>
<td>Clozapine 64, Olanzapine 63</td>
<td>Clozapine 47, Olanzapine 50</td>
</tr>
<tr>
<td>Tollefson 2001, N = 180</td>
<td>Clozapine 35, Olanzapine 38</td>
<td>Clozapine 32, Olanzapine 46</td>
<td>Clozapine 16, Olanzapine 27</td>
</tr>
</tbody>
</table>

**Pooled Relative Risk (95% CI)**
Q = 0.30 (df = 1) P = 0.59
Q = 0.87 (df = 1) P = 0.09
Q = 0.80 (df = 1) P = 0.18

(Table 11: Ref.: McDonagh MS et al, 2010)

(Table 12: Ref.: McDonagh MS et al, 2010)
2.19. Tolerability and Adverse Events of Atypical Antipsychotics

The atypical antipsychotics have differing adverse event profiles, both in short- and long-term. Here, adverse events that relate to the tolerability of the drugs are reviewed for the population of patients with schizophrenia. The adverse events focused on here are the overall rate of withdrawal from studies due to adverse events, extrapyramidal symptoms and metabolic abnormalities such as weight gain and lipid abnormalities under study conditions.

2.19.1. Tolerability of Atypical Antipsychotics: Shift in Risk Perception

Prior Safety Concerns

Current Safety Concerns

2.19.2. Atypical Antipsychotics and Extrapyramidal Symptoms

In CATIE Phase I study, no differences were found between olanzapine, quetiapine, risperidone, or ziprasidone in the incidence of extrapyramidal symptoms (EPS) identified as an adverse event or akathisia or movement disorders based on rating scales. Similarly, no differences were found between drugs in the subsequent CATIE Phase Ib, Phase 2E, or Phase 2T, nor in another trial with multiple drugs (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone). In a more detailed analysis of only treatment-emergent EPS among patients in CATIE, differences in incidence or severity between the atypical antipsychotic drugs were not found based on rating scales for parkinsonism, dystonia, akathisia, or tardive
dyskinesia. The use of antiparkinsonism medications was found greater with risperidone and lower with immediate-release quetiapine (P=0.029), and lower rates of discontinuation due to Parkinsonism symptoms were found with immediate-release quetiapine and ziprasidone (P<0.05, rates not reported). (McDonagh MS et al, 2010)

In a 52-week trial by McEvoy JP et al (2007) of olanzapine, quetiapine and risperidone, no statistically significant differences were found between the drugs in proportions of patients with mild or worse EPS. This study did find statistically significantly more patients taking olanzapine (11%) required anticholinergic medication for EPS compared with quetiapine (4%) (P = 0.021) Data or analysis for comparison on quetiapine and risperidone were not reported. In a study of patients with acute schizophrenia by McCue RE et al (2006), conducted in the inpatient setting over 3 weeks found no statistically significant difference in symptom scores among aripiprazole, haloperidol, olanzapine, quetiapine, risperidone or ziprasidone This study reported that 30% of patients taking risperidone and 10% taking quetiapine or ziprasidone required anticholinergic medication for EPS, while no patient taking olanzapine or aripiprazole required anticholinergic medication for EPS (McDonagh MS et al, 2010)

In head-to-head trials comparing only 2 drugs, differences were not found between olanzapine and quetiapine in 3 studies, clozapine and olanzapine in 4 studies, or olanzapine and aripiprazole in 2 studies. In most cases, some proportion of patients entering the trials had pre-existing extrapyramidal symptoms, such that measures were actually improvements from baseline. Very few trials were specific about measuring new-onset extrapyramidal symptoms as a treatment emergent adverse event (McDonagh MS et al, 2010)

For all other comparisons made in head-to-head trials, at least some differences were found. Of 10 studies of olanzapine and risperidone (2223 patients total) reporting extrapyramidal symptom adverse event data, 8 found no differences between the drugs, while 2 (586 patients total) found risperidone to have higher rates or worsening symptoms of extrapyramidal symptoms on measures reflecting akathisia, dyskinesia, dystonia, pseudoparkinsonism, and overall extrapyramidal symptoms. Mean doses of risperidone 5 and 7 mg were compared with olanzapine 13 and 17 mg of olanzapine, respectively. Across these studies, size and quality ratings were similar. One good-quality, short-term trial (N = 377) was statistically powered to determine a difference in extrapyramidal adverse event reports and found no differences between the groups on this measure assessed on Extrapyramidal Symptom Rating Scale (ESRS) scores or use of anticholinergic medications. In this trial the mean dose of olanzapine was below midrange, while the mean dose of risperidone was near the midpoint (5 mg). The other good-quality trial found treatment-emergent and worsening pre-existing extrapyramidal symptoms in 28.9% (N=35) of olanzapine patients and 50.4% (N=61) of risperidone patients (P=0.0006). Dosing in this study also had olanzapine slightly below midrange and
risperidone within midrange. A 13-week study of risperidone long-acting injection compared with olanzapine found statistically significantly higher rates of extrapyramidal symptoms with risperidone (25% compared with 15%, \( p < 0.05 \)). Rates of discontinuation due to these effects were not different between the groups. (McDonagh MS et al, 2010)

In a retrospective study of pharmacy records, new users of haloperidol, olanzapine, and risperidone were identified. Prescriptions for antiparkinson drugs taken during the first 90 days of atypical antipsychotic use were analyzed using a Cox proportional hazards model adjusting for potential confounders. The analysis compared olanzapine and risperidone to haloperidol. Both drugs resulted in a lower risk for starting antiparkinson drugs even after considering prior antipsychotics and antiparkinson drug use. Although the reduction in risk was numerically greater with olanzapine, direct analysis was not conducted and the confidence intervals overlapped. (McDonagh MS et al, 2010)

In 5 studies comparing clozapine with risperidone, risperidone was found to have fewer patients with a score of "0" on pseudoparkinsonism symptoms in 1 study. Yet differences were not found on 6 other measures of extrapyramidal symptoms, and higher rates of use of anticholinergic medications with higher doses of risperidone were found in another study. The strength of the evidence on extrapyramidal symptoms in comparisons of clozapine and risperidone is severely hampered by the dose inequities, usually higher doses of risperidone (> 6 mg/d) and lower doses of clozapine than typically used. In 1 study the difference in use of anticholinergic medications at the higher but not the lower dose of risperidone supports the dose-response relationship between extrapyramidal symptoms and risperidone. In a point-prevalence study including patients who had been on a stable dose of clozapine or risperidone for 3 months, risperidone was found to have much higher rates of extrapyramidal symptoms (akathisia, rigidity, cogwheeling) than clozapine. It is unknown how long patients were taking each of the drugs prior to the 3-month period, what other antipsychotics they had taken prior to the atypical antipsychotic, and the dropout rate during the 3-month period due to extrapyramidal symptoms. Analyses did not control for these and other potential confounding factors. (McDonagh MS et al, 2010)

Four studies comparing clozapine with olanzapine assessed extrapyramidal symptoms. One found a difference when comparing the mean change in SAS (Simpson Angus Scale) score from baseline to endpoint (-1.4 for clozapine, -3.2 for olanzapine). Other measures of extrapyramidal symptoms were not different between the drugs in this trial. Mean doses in this trial were lower than midpoint for clozapine and within midrange for olanzapine, which may have had an impact of these results. The other studies found no differences between the drugs in extrapyramidal symptoms outcomes. Three of 4 studies of quetiapine and risperidone found measures of extrapyramidal symptoms to be worse with risperidone. In 1 study of risperidone and aripiprazole, the number of patients with treatment-emergent extrapyramidal symptoms...
was numerically greater with risperidone (24% compared with 12%), but statistical analysis was not undertaken due to the small size of the study (N=85). Similarly, in a study of risperidone and ziprasidone, risperidone was found to have higher scores on akathisia and movement disorder, and higher proportions of patients reporting extrapyramidal symptoms as an adverse event. These studies are not consistent in the specific measure of extrapyramidal symptoms on which risperidone was worse; in some, scores on akathisia and treatment-emergent extrapyramidal symptoms were worse, while in others scores on involuntary movements were worse. Two of 3 studies comparing ziprasidone and olanzapine found ziprasidone to have worse extrapyramidal symptoms outcomes. One found higher scores on ratings of akathisia, while the other found higher scores on ratings of involuntary movements (McDonagh MS et al, 2010).

2.19.3. Schizophrenia and the Metabolic Risk Factors

Persons with schizophrenia have a 20% shorter life expectancy than the general population. (Newman, 1991; Bartel, 2004) Regardless of antipsychotic use, schizophrenia patients are at greater risk of developing diabetes and cardiovascular disease than the general population. Table 13:

<table>
<thead>
<tr>
<th>Smoking</th>
<th>5x more likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Inactivity</td>
<td>½ as likely to do light exercise</td>
</tr>
<tr>
<td></td>
<td>¼ as likely to do vigorous exercise</td>
</tr>
<tr>
<td>Overweight/Obese</td>
<td>8x more likely</td>
</tr>
<tr>
<td>Alcohol Consumption</td>
<td>2x as likely to abstain</td>
</tr>
<tr>
<td></td>
<td>4x more likely to drink harmful amounts</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.5–2x greater prevalence</td>
</tr>
<tr>
<td>Family History of Diabetes</td>
<td>6x more likely</td>
</tr>
</tbody>
</table>

Table 13. Ref Cited by Walid S, 2010

2.19.4. Atypical Antipsychotics and Cardiometabolic Risk

Atypical antipsychotics may add to the health burden of schizophrenia by causing weight gain, impaired glucose metabolism, and hyperlipidemia (Newcomer JW, 2005) People with schizophrenia die prematurely from comorbid physical diseases, particularly from cardiometabolic disturbances. Although some host vulnerability exists, there is also mounting evidence of a relationship between metabolic disturbances and antipsychotic medications. (Buckley et al, 2008)

- The atypical antipsychotics vary in prevalence of associated weight gain, diabetes, and dyslipidemia.
- Proposed mechanisms of action of atypical antipsychotic-induced cardiometabolic risk
  - Increase appetite → weight gain
  - Reduce insulin release by blocking M₃ receptors on beta cells
  - Insulin resistance (unknown mechanism)

(ADA-APA-AACE-NAASO, 2004)
Baseline data of subjects with chronic schizophrenia treated with various antipsychotics from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) showed a prevalence of metabolic syndrome of 42.7%, doubling that seen in the general population. (Cindy PY Chiu et al., 2011)

Alongside the efficacy debate, recently there has been considerable interest and concern about the metabolic abnormalities associated with atypical antipsychotic use (ADA-APA-AACE-NAASO, 2004). The issues being discussed are whether these metabolic abnormalities are seen only with antipsychotic treatment, if there is a difference between atypical and conventional antipsychotics in terms of these side effects, and about the differing metabolic profiles of the various atypical antipsychotics. (Kannabiran and Singh, 2008)

**Table 14: Metabolic Side Effects of Atypical Antipsychotics.** (ADA-APA-AACE-NAASO, 2004)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight gain</th>
<th>Risk for diabetes</th>
<th>Worsening lipid profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone*</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+ = increase effect, − = no effect, D = discrepant results. *Newer drugs with limited long-term data.
2.19.5. The Prevalence of Obesity, Diabetes, and Dyslipidemia Differs Among the Atypical Antipsychotics (SGAs):

Although the use of atypical antipsychotics offers many benefits and may reduce some of the factors related to the morbidity and mortality of schizophrenia, these drugs appear to be associated with varying degrees of metabolic adverse effects, such as weight gain, impaired glucose metabolism, dyslipidemia and in some cases, more serious morbidity, such as cardiovascular disease. (Nasrallah HA, 2008)

Almeras et al (2004) studied anthropometric and metabolic indices associated with atypical antipsychotic treatment, in an open-label, cross sectional, multi-center study. Patients treated with risperidone (n=45) or olanzapine (n=42) as their 'first and only' antipsychotic were studied. Compared to the reference group, patients treated with the atypical antipsychotics had elevated fasting blood sugar, insulin levels and insulin resistance. The study revealed significant differences between olanzapine and risperidone. Patients treated with olanzapine had a significantly worse metabolic profile compared to those treated with risperidone, with more than a third of the former group exhibiting a 'hypertriglyceridemic waist' (waist circumference ≥ 90 cm, triglycerides ≥ 2.0 mmol/L).

2.19.6. Mechanism Underlying Antipsychotic Induced Metabolic Abnormalities

In responding to the paper - retrospective case series by Meyer (2001), Baptista et al (2002a) suggest that insulin resistance plays a significant part in development of type 2 diabetes mellitus. They postulate that excess body weight results in insulin resistance, which results in decreased availability of glucose to peripheral tissues. Lipids are mobilized from body stores to meet energy demand and results in hyperlipidemia. The authors stress that causation of hyperlipidemia is multi-factorial, with insulin resistance being an important cause. They designed a 'composed ratio' (CR) which included the absolute affinity of antipsychotics for neurotransmitter receptors involved in regulation of food intake. Clozapine and olanzapine had the highest CR. However the author disagrees observing that increase in triglyceride and cholesterol levels did not correlate with BMI, baseline weight, baseline fasting glucose or degree of weight gain (Meyer 2001).

2.19.7. Weight Gain by Atypical Antipsychotics

Weight gain is emerging as one of the most significant side effects associated with atypical antipsychotic therapy Allison DB et al, 1999, Wirshing DA et al, 1999, Ganguli et al, 1999). Weight gain is associated with an increased risk of diabetes mellitus and hyperlipidemia (all associated with an increased risk of coronary heart disease), and there are increasing reports of these complications in patients with schizophrenia receiving atypical antipsychotics (Tandon and Jibson, 2003).
As reported by Tandon and Jibson (2003), the relative propensity to cause weight gain among the newer generation antipsychotics is as follows:

\[
\text{clozapine} > \text{olanzapine} > \text{risperidone} = \text{quetiapine} > \text{ziprasidone} = \text{aripiprazole}.
\]

The average weight gain with 1-year treatment ranges from 33 lbs (clozapine) to 2 lbs (aripiprazole, ziprasidone), with olanzapine (25 lbs) and risperidone and quetiapine (4–8 lbs) in between. Long-term weight gain is of greater clinical relevance than short-term gain, as patients with schizophrenia require chronic antipsychotic therapy. (Newcomer JW, 2005)

ADA-APA-AACE-NAASO (2004) recommends careful consideration of metabolic risk when starting a SGA. If a patient gains ≥ 5% of initial weight and/or develops worsening glycemia or dyslipidemia during therapy, an assessment of therapy should be considered.

2.19.8. Pathogenesis of Weight Gain by Atypical Antipsychotics

Obesity and weight gain are the result of a complex confluence of environmental, behavioural, genetic, and neurochemical factors. (McIntyre RS, 2001) Atypical antipsychotics (AAs) differ in their ability to induce weight gain, and in the duration of this effect. This presumably reflects differences in their pharmacological properties, and calls into question the mechanisms by which these agents act on body weight regulation. At present, these remain unclear, although it seems likely that multiple mechanisms are involved (Chue P, Cheung R., 2004). AAs (atypical antipsychotics) exhibit pleiotropic receptor affinity (Bymaster FP et al, 1999). Many, but not all, patients experiencing weight gain with antipsychotic drugs report increased appetite, binge eating, carbohydrate craving, food preference changes, and decreased satiety. (McIntyre RS, 2001)

a) Antiserotonergic effects

The serotonergic system in the lateral hypothalamus appears to play a key role in regulating food intake and agonists of different 5-HT receptor subtypes have been shown to decrease feeding in animal models (Casey DE et al, 2001). Atypical antipsychotics have a variety of antagonistic effects at 5-HT receptors, and a
correlation has been reported between antagonist potency at 5-HT2A-2C receptors (which is associated with increased appetite) and body weight gain (Baptista T, 2002b cited by Chue P, Cheung R., 2004) Tecott and others (1995) bred a strain of mice, genetically deficient in 5-HT2C receptors, that became obese and had a propensity for seizures. Fenfluramine and m-chlorophenylpiperazine (m-CPP), both 5-HT2C agonists, have been shown to suppress appetite and decrease food intake in humans (Garattini S et al 1989, Goodall E 1998, Walsh AES et al, 1994, cited by McIntyre RS 2001) Further, the 5-HT2A/C receptor is antagonized to varying degrees with the existing AAs (Bymaster FP 1999, Schotte A 1996, cited by McIntyre RS 2001).

b) Antidopaminergic effects

Stimulation of dopamine D2 receptors in the brain is associated with decreased food intake Most antipsychotic drugs act as D2-receptor antagonists, and there is a significant correlation between this antagonist activity and antipsychotic effect (Seeman and Kapur S, 2000. cited by Chue P and Cheung R., 2004) However, there is no clear evidence for a relationship between the D2-receptor antagonist activity of atypical antipsychotics and the extent of weight gain (Wetterling T, 2001 cited by Chue P and Cheung R., 2004)

c) Antinoradrenergic effects

Noradrenergic receptors also appear to play a role in appetite and body weight control. Blockade of α- and β-noradrenergic receptors is associated with weight gain, although the β2-receptor has been shown to decrease food intake and increase energy expenditure. Mutations of the β3 receptor gene have been associated with the development of weight gain and type 2 diabetes mellitus and it is possible that a similar genetic predisposition may exist in schizophrenia, increased expression of genes coding for the β3 and α1a receptors has been reported in patients with schizophrenia treated with clozapine (Chue P, Cheung R., 2004)

d) Antihistaminergic effects

It is well known that antihistaminergic agents stimulate appetite and weight gain in humans, and hence it seems likely that the antihistaminergic properties of atypical antipsychotics contribute to their effects on body weight. The available agents, however, differ markedly in their capacity for binding to histamine H1 receptors. Drugs such as clozapine, olanzapine and zotepine show a higher affinity for histamine H1 receptors than for serotoninergic or dopaminergic receptors; hence, binding to these receptors is likely to be highly relevant to the weight gain associated with these compounds. By contrast, risperidone has a lower affinity for H1 receptors than for dopaminergic or SHT2A receptors (Chue P, Cheung R., 2004)

Wirshing (1999) noted an exponential relation between antipsychotic-induced weight gain and histamine-1 receptor (H1) affinity. Clozapine exhibits histamine blockade affinity more than 20-fold greater than risperidone (Mcintyre RS, 2001)
### Table 15. Weight gain and binding data for typical and atypical antipsychotics (Ref Kroeze WK et al, 2003)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Weight gain (kg/10 weeks)</th>
<th>S-HT₁₂</th>
<th>S-HT₂₃</th>
<th>D₂</th>
<th>H₁</th>
<th>M₃</th>
<th>α₁</th>
<th>α₂</th>
<th>α₅Β</th>
<th>α₅C</th>
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<th>S-HT₄</th>
<th>S-HT₇</th>
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<td>Anpiprazole</td>
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<td>0.71</td>
<td>22.4</td>
<td>8.7</td>
<td>0.66</td>
<td>29.7</td>
<td>4677</td>
<td>26</td>
<td>74</td>
<td>102</td>
<td>37</td>
<td>557</td>
<td>7832</td>
<td>96</td>
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<tr>
<td>Chlorpromazine</td>
<td>T</td>
<td>2.1</td>
<td>25</td>
<td>8</td>
<td>4</td>
<td>6</td>
<td>47</td>
<td>0.28</td>
<td>184</td>
<td>27</td>
<td>46</td>
<td>1164</td>
<td>201</td>
<td>358</td>
</tr>
<tr>
<td>Clozapine</td>
<td>A</td>
<td>4</td>
<td>17</td>
<td>5.4</td>
<td>25.6</td>
<td>12</td>
<td>25</td>
<td>1.64</td>
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<td>26</td>
<td>34</td>
<td>1048</td>
<td>17</td>
<td>179</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>T</td>
<td>0.43</td>
<td>1386</td>
<td>30</td>
<td>0.54</td>
<td>21</td>
<td>1441</td>
<td>6.5</td>
<td>314</td>
<td>81.6</td>
<td>28.8</td>
<td>1457</td>
<td>38</td>
<td>8</td>
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<tr>
<td>Haloperidol</td>
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<td>0.48</td>
<td>10000</td>
<td>53</td>
<td>4</td>
<td>1800</td>
<td>10000</td>
<td>12</td>
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<td>550</td>
<td>1202</td>
<td>3666</td>
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<tr>
<td>Loxapine</td>
<td>A</td>
<td>0.75</td>
<td>5.5</td>
<td>7.7</td>
<td>12</td>
<td>7</td>
<td>122</td>
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<td>79.9</td>
<td>2456</td>
<td>32.9</td>
<td>872</td>
</tr>
<tr>
<td>Molindone</td>
<td>T</td>
<td>-1.06</td>
<td>10000</td>
<td>320</td>
<td>63</td>
<td>2130</td>
<td>10000</td>
<td>2612</td>
<td>1097</td>
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<td>1726</td>
<td>3797</td>
<td>1008</td>
<td>3033</td>
</tr>
<tr>
<td>Olanzapine</td>
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<td>58</td>
<td>2</td>
<td>34</td>
<td>2</td>
<td>105</td>
<td>1.15</td>
<td>314</td>
<td>81.6</td>
<td>28.8</td>
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<td>1024</td>
</tr>
<tr>
<td>Perphenazine</td>
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<td>132</td>
<td>5.6</td>
<td>1.4</td>
<td>8</td>
<td>1848</td>
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<tr>
<td>Pimozide</td>
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<td>-3.53</td>
<td>3350</td>
<td>19</td>
<td>0.65</td>
<td>692</td>
<td>1955</td>
<td>1977</td>
<td>1593</td>
<td>8211</td>
<td>3765</td>
<td>650</td>
<td>71</td>
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<tr>
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<td>2502</td>
<td>101</td>
<td>245</td>
<td>11</td>
<td>10000</td>
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<td>28</td>
<td>4316</td>
<td>1865</td>
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<tr>
<td>Risperidone</td>
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<td>1.67</td>
<td>35</td>
<td>0.17</td>
<td>6.5</td>
<td>15</td>
<td>10000</td>
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<td>13</td>
<td>4275</td>
<td>1188</td>
<td>6.6</td>
</tr>
<tr>
<td>Sertindole</td>
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<td>0.9</td>
<td>0.58</td>
<td>91</td>
<td>130</td>
<td>2692</td>
<td>18</td>
<td>640</td>
<td>450</td>
<td>450</td>
<td>280</td>
<td>54</td>
<td>28</td>
</tr>
<tr>
<td>Thioridazine</td>
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<td>2.81</td>
<td>100</td>
<td>10</td>
<td>11</td>
<td>19</td>
<td>43</td>
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<td>748</td>
<td>1807</td>
<td>75.1</td>
<td>99</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>T</td>
<td>2.81</td>
<td>100</td>
<td>50</td>
<td>0.63</td>
<td>4</td>
<td>10000</td>
<td>11</td>
<td>799</td>
<td>502</td>
<td>519</td>
<td>4104</td>
<td>2084</td>
<td>15.5</td>
</tr>
<tr>
<td>Trifluoperazine</td>
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<td>0.34</td>
<td>378</td>
<td>13</td>
<td>1.3</td>
<td>63</td>
<td>10001</td>
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<td>6537</td>
<td>1636</td>
<td>3915</td>
<td>950</td>
<td>118</td>
<td>2908</td>
</tr>
</tbody>
</table>

* A: atypical, T: typical  ¹Data from Alston et al (1999, p 24) for later classification purposes, values in bold face were coded as 'no weight gain' and values in normal type were coded as 'weight gain'.

The molecular mechanism(s) responsible for antipsychotic drug-induced weight gain are unknown, but have been hypothesized to be because of interactions of antipsychotic drugs with several neurotransmitter receptors, including 5-HT₂₃ and 5-HT₂₅ serotonin receptors, H₁-histamine receptors, α₁- and α₂-adrenergic receptors, and m₃-muscarinic receptors. To determine the receptor(s) likely to be responsible for antipsychotic-drug-induced weight gain, authors screened 17 typical and atypical antipsychotic drugs for binding to 12 neurotransmitter receptors. The discriminant function analysis, as well as the affinity for the H₁-histamine receptor alone, correctly classified 15 of the 17 drugs into two groups; those that induce weight gain and those that do not. Taken together, these results clearly indicate that antipsychotics drugs with high H₁-histamine receptor affinities are associated with significant weight gain. It is also clear that mechanisms other than H₁-histamine receptor blockade can also induce weight gain. Thus sulpiride, a selective D₂/D₃ antagonist, has virtually no affinity for H₁-histamine receptors (Roth et al, in preparation), yet it induces significant long-term weight gain among individuals with schizophrenia. Similarly, haloperidol and fluphenazine have relatively low H₁-histamine receptor affinities, yet, when given in depot formulations, have been reported to induce substantial weight gain (Taylor and McAskill, 2000). In this regard, it is interesting to note that the discriminant functions analysis predicts that fluphenazine will induce weight gain. Thus, factors independent of H₁-histamine receptor affinity may contribute to weight gain induced by typical and atypical antipsychotic drugs. Because centrally acting H₁-histamine receptor antagonists are known to induce weight gain with chronic use, and because H₁-histamine receptor affinities are positively correlated with weight gain among typical and atypical antipsychotic drugs, it was recommended that the next generation of atypical antipsychotic drugs be screened to avoid H₁-histamine receptors.
Review of Literature

e) Prolactin
It has also been hypothesized that prolactin elevation may stimulate feeding centres in the brain by changing
the estrogen–testosterone ratio (Wang DY et al, 1987), which in turn modifies the functioning of satiety-
related neurons in the ventral medial and paraventricular hypothalamus (Baptista T et al, 1999). Further, in
vitro experiments have demonstrated adipocyte insulin insensitivity in hyperprolactinemic conditions
(Cabrera R, 1988). However, evidence militating against prolactin elevation as a sufficient mechanistic
variable is the absence of sustained prolactin elevation with clozapine and olanzapine. (Dickson RA et al,
1999) (cited by McIntyre RS, 2001)

f) Leptin
Several peptides have been implicated in the control of appetite, including leptin. Leptin is a hormone
derived from adipose tissue that plays an important role in the development of obesity and eating disorders.
Leptin, released by adipocytes, is believed to act at the level of the hypothalamus, modulating appetite,
energy expenditure, and the neuroendocrine axis. It has been reported that serum leptin concentrations
correlate positively with BMI and per cent age of body fat. Severe obesity has been reported in subjects
genetically deficient in leptin and in animals with defective leptin receptors. (Montague CT et al, 1997) The
administration of leptin in both clinical and preclinical samples is variously reported to reduce obesity.
Although leptin increases may be a product of weight gain, its etiopathogenetic contribution and influence on
symptom change are under investigation (cited by McIntyre RS, 2001)

Influences on leptin levels by clozapine, olanzapine, haloperidol, and valproic acid have been reported
weeks) treatment with atypical antipsychotics results in significant increases in circulating leptin
concentrations, whereas haloperidol has no such effect. The magnitude of this effect varies between agents:
olanzapine and clozapine increase leptin concentrations to a similar extent, whereas quetiapine has less
effect than olanzapine. A further study found a correlation between serum leptin concentrations and weight
gain during long-term treatment with atypical antipsychotics, patients receiving olanzapine showed the
highest concentrations, whereas risperidone-treated patients had the lowest concentrations. (Chue P,
Cheung R, 2004)

Fabio et al. (2012) recently reviewed the role of leptin in antipsychotic induced weight gain. Several lines of
research indicate that leptin could be a good candidate involved in pathways linking antipsychotic treatment
and weight gain. Leptin is a circulating hormone released by adipocytes in response to increased fat
deposition to regulate body weight, acting through receptors in the hypothalamus. In this work, they
reviewed preclinical, clinical, and genetic data in order to infer the potential role played by leptin in
antipsychotic-induced weight gain considering two main hypotheses. (i) leptin is an epiphenomenon of
weight gain; (ii) leptin is a consequence of antipsychotic-induced “leptin-resistance status,” causing weight
A majority of research has focused on the effects of clozapine and olanzapine on SLL (serum leptin levels). The positive modulation of this parameter by the studied atypical antipsychotics has been observed as early as a few hours after the beginning of the treatment, peaking between 6 and 10 weeks after, and remaining elevated for a period of up to several months. With respect to atypical AP treatment, a number of studies found elevated leptin levels following atypical AP (antipsychotic) medications, in some cases independent of BMI increase. Olanzapine and clozapine therapy predominantly occurs over the first 6 months of treatment plateauing after 6 months to 1 year of treatment, leptin changes do not parallel with weight changes during extended AP treatment as pointed out by Bromel et al. (1998). In contrast to olanzapine and clozapine, fluctuations in SLL have not been seen in risperidone treatment, which is consistent with the conventional neuroleptic treatment causing less fluctuation in BW. Further research is still needed to clarify the relationship between leptin and antipsychotics.

**g) Glucose Transporters**

There has been some effort to clarify the effects of antipsychotic drugs on glucose transporters, and specifically transporters within the rat pheochromocytoma cell line, a neuronal cell line which participates in glucose uptake and transport via glucose transporter proteins (GLUTs) in the cells. The thought was that drugs such as olanzapine and clozapine might share an affinity for dopamine receptors in rat pheochromocytoma cells, and that upon binding to these dopamine receptors, interfere with glucose uptake, seen clinically as insulin resistance. The problem is that the results have been inconsistent with respect to the dopamine D₂ receptor, with some drugs, like haloperidol, that have a very high affinity for this receptor, having minimal effect on glucose uptake whereas others with high affinity, like fluphenazine, having strong inhibitory effects. The atypical antipsychotic clozapine, which has a strong affinity for D₄ also affected glucose transport strongly. Whether the mechanism by which these medications affect these cells involves dopamine receptors or some other site (calcium channels have also been proposed) requires further research. (Ferrailoli et al., 2004)

**h) Insulin resistance**

Insulin resistance forms part of a cluster of cardiovascular risk factors, together known as the metabolic syndrome or syndrome X, which is believed to contribute to the development of coronary artery disease and diabetes. Some atypical antipsychotics, notably clozapine and olanzapine, have been shown to increase insulin resistance (cited in Chue P, Cheung R., 2004)

Collectively, data from several research paradigms converge and suggest that atypical antipsychotic-induced weight gain or obesity is mechanistically related to an as-yet-undetermined interplay of multiple neurotransmitter and receptor interactions, with resultant changes in appetite, energy intake, and feeding
behaviour. Novel research paradigms refining putative mechanistic links between atypical antipsychotics and neuropeptides are underway. (McIntyre RS, 2001)

i) Genetic determinants for antipsychotic-induced metabolic abnormalities

However, not all patients experience antipsychotic-induced adverse effects to the same extent. This high interindividual variability suggests that genetic variability importantly contributes to a person's susceptibility to weight gain and the metabolic syndrome, making it a target for pharmacogenetic studies. (Risselada A, 2012)

Of the genetic risk factors for antipsychotic-induced metabolic dysregulation, only those associated with weight gain have been investigated to any extent. The strongest evidence lies with the -759C/T polymorphism of the serotonin (5-hydroxytryptamine) 5-HT$_{2c}$ receptor gene for which an association with antipsychotic-induced weight gain has been identified. This has some a priori validity since antagonism at the 5-HT$_{2c}$ receptor is likely to be a mechanism contributing to this side-effect of antipsychotic drug treatment. A further gene showing an association with drug-induced weight gain is that for leptin; the functional promoter polymorphism-2548A/G is also associated with long-term development of antipsychotic drug-induced weight gain. Leptin is an important hormone regulating adipose tissue mass and body weight; it inhibits food intake and stimulates energy expenditure. Thus, although there is no report of a direct genetic association with development of metabolic syndrome in patients treated for schizophrenia, 5-HT$_{2c}$ receptor and leptin gene polymorphisms provide strong candidates. (Yevtushenko et al., 2008)

Another likely candidate gene for an association with antipsychotic-induced metabolic adverse effects is the ADRA2A gene coding for the adrenergic $\alpha_{2A}$ receptor, because studies have consistently found associations between polymorphisms within this gene and antipsychotic-induced weight gain as well. (Risselada A, 2012)

Whatever the underlying mechanisms, findings of study ‘the influence of 5-HT2C receptor and leptin gene polymorphisms, smoking and drug treatment on metabolic disturbances in patients with Schizophrenia’ by Yevtushenko et al., highlight the importance of interacting genetic factors in determining both obesity and metabolic syndrome in patients with schizophrenia and thus indicate the possible mechanisms underlying antipsychotic-induced metabolic disturbances and the potential for genetic identification of ‘high risk’ individuals. (Yevtushenko et al., 2008)

2.19.9. Weight Gain under Trial Conditions - Studies:

In one of the most cited comprehensive review of research literature by Allison D.B et al (1999) estimated and compared the effects of both typical and atypical antipsychotics on weight gain, using a very thorough search methodology. This was followed by metaanalysis with the estimated mean weight change calculated
using both fixed and random effects models. For patients on standard doses for 10 weeks, the authors calculated point estimates of weight gain for each drug. Weight gain associated with five atypical antipsychotics was examined in the study – ziprasidone(0.04 kg), risperidone(2.10 kg), sertindole(2.92 kg), olanzapine(4.15 kg) and clozapine(4.45 kg). Weight change induced by risperidone was intermediate between the group of antipsychotics associated with low or no risk of weight gain (molindone -0.39 Kg; ziprasidone +0.04 kg) and the group of drugs associated with high risk (thioridazine +3.19; olanzapine +4.15 kg, clozapine +4.45). Subjects receiving placebo lost weight in the range of 0.74 kg. Though the two conventional antipsychotics molindone and pimozide were associated with weight loss, the effects were not significant at 10 weeks. The study indicated that patients may gain more than 5% of initial body weight, with the weight gain becoming more pronounced with time, with the attendant risks for the general physical health of the patient. (Allison D.B. et al, 1999)

**Figure 29:** 95% Confidence Intervals For Weight Change After 10 Weeks on Standard Drug Doses, Estimated From a Random Effects Model. (Allison DB et al, 1999)

In a five year naturalistic study of 82 patients treated with clozapine (Henderson et al. 2000), weight gain and onset of diabetes were studied at 6 monthly intervals. 36.6% of patients developed diabetes, with 61.7% of the study population experiencing at least one episode of elevated fasting blood glucose. The age of the patients significantly correlated with risk of developing diabetes. All 82 patients in the study gained significant weight over time, this being greatest in the first 12 months, though continuing till 46 months. Serum triglycerides increased significantly as well. The limitations of the study included not being able to examine the role of risk factors such as ethnicity, family history or exercise. (Henderson et al. 2000)

Sheitman et al. (1999) re-examined the lipid profile of 9 patients with schizophrenia, after initiating treatment with olanzapine. Though they did not observe a change in cholesterol or lipoprotein levels, the level of triglycerides increased from a mean of 170 mg/dl to 240 mg/dl. Olanzapine was found to be associated with a significant risk of diabetes compared to risperidone in a large population based nested
case-control study. Zipursky et al (2005) analysed data from a multi-centre randomized controlled trial of patients with first-episode psychosis, treated with olanzapine or haloperidol. Clinically significant weight gain was defined as ≥7% increase in weight (kg) from baseline. In olanzapine-treated patients, the BMI at baseline, 12 weeks, 1 year and 2 years was 23.6, 26, 27 and 27 respectively. In the haloperidol treated patients, BMI at corresponding periods in time was 23.9, 24.8, 25.3 and 25.3. Clinically significant weight gain occurred significantly faster in the olanzapine group compared to the haloperidol group. 36.7% and 40.8% of patients on olanzapine, and 20.5% and 35.9% of haloperidol treated patients were obese or overweight respectively. Subjects from the ethnic minority population demonstrated clinically significant weight gain, independent of treatment group.

Results from the CATIE study show that clozapine and olanzapine produce substantial weight gain and an increased risk of associated metabolic disturbances. Risperidone and quetiapine produce intermediate changes in mean weight in comparison with other atypical antipsychotics, and are associated with an uncertain metabolic risk, while aripiprazole and ziprasidone produce minimal or no weight gain and carry no risk for adverse metabolic changes (Lieberman JA et al, 2005).

Ascher-Svanum et al (2005) say that weight gain has been considered a prognostic indicator even before the introduction of antipsychotics. They hypothesized that weight gain was a marker of improvement in psychopathology, that weight gain observed with placebo would be associated with clinical improvement and that antipsychotics differing in weight gain liability differed in effectiveness. By using data from randomized controlled trials and metaanalyses, they undertook post hoc analysis and demonstrated that greater weight gain was significantly correlated with better therapeutic response. The authors used data from studies which did not measure weight gain as a primary outcome measure. In a randomized controlled trial examining the efficacy and safety of olanzapine and haloperidol in 263 patients with first-episode psychosis (Lieberman JA et al, 2003), significant side effects were observed in patients treated with olanzapine. In this group of patients, the mean weight gain was 7.3 kg, with 61.5% of patients gaining more than 7% of their body weight (compared to 22.7% in the haloperidol treated group) and their BMI increasing by 2.39 (compared to 0.88 of patients receiving haloperidol), with these findings being highly significant.

In one Indian double-blind prospective study by Saddichha S et al (2007) in previously drug-naive schizophrenia patients, 31.81% prevalence of obesity, 10.1% incidence of obesity (Saddichha S et al, 2008a), and 18.2 per cent prevalence of metabolic syndrome (Saddichha S et al, 2008b) after 6-weeks of treatment with antipsychotics has been reported (Cited by Padmavati R, 2010) Weight change was observed in 80 outpatients receiving olanzapine by Jain et al (2006), 66.6% of the patients had weight gain over a period of 4 weeks which was not related to the dose of the drug or BMI.
In a prospective study of 48 weeks by Ananth J et al (2000) the weight gain in 66 patients treated with olanzapine, risperidone, ziprasidone or haloperidol were compared. At the end of the study, the mean weight gains with the four drugs were approximately 5.4, 2.5, 1.9 and 1 kg, respectively.

In a prospective study by Conley RR et al (2001), 377 patients received flexible doses of risperidone 2–6 mg, or olanzapine 5–20 mg, for 8 weeks. Risperidone was associated with significantly less weight gain than olanzapine (mean 1.5 vs. 3.3 kg, respectively, P<0.001), and significantly fewer patients experienced a weight gain of 7% or more with risperidone (12 vs 27%, P<0.001). Moreover, in risperidone-treated patients, weight gain was mainly seen in patients with a low body mass index (BMI) at baseline, whereas with olanzapine weight gain occurred irrespective of the patients’ baseline BMI.

There are, however, other data suggesting that olanzapine-related weight gain may be greatest in patients with the lowest BMI. The combined data from four studies showed that 41% of a total of 1455 olanzapinetreated patients experienced clinically significant weight gain (>7%), the incidence of weight gain was highest (32%) among patients who were underweight at baseline and lowest (11%) among those who were overweight (Beasley CM et al, 1997). A prospective study by Barak Y (2002) measured body weight in 180 elderly schizophrenic patients before and after 1 year’s treatment with risperidone, at a mean dose of 3.7 mg/day. No significant weight gain occurred in these patients during risperidone treatment.

2.19.10. Weight gain in Naturalistic and Observational Studies:

As reviewed by McDonagh MS et al (2010), the effects of atypical antipsychotic drugs on weight gain in observational studies was somewhat smaller than seen in clinical trials, but the differences between the drugs remained.

The effects on weight gain of olanzapine, risperidone and haloperidol were compared in a large prospective naturalistic study involving a total of 2967 patients (Gomez JC et al, 2000). The incidence of weight gain, reported as a treatment-emergent adverse event, during the first 6 months of treatment was significantly higher with olanzapine (6.9%) than with risperidone (1.9%, P=0.001 vs. olanzapine) or haloperidol (0.9%, P=0.013). (Chue P, Cheung R., 2004)

In a five year naturalistic study of 82 patients treated with clozapine (Henderson et al 2000), weight gain and onset of diabetes were studied at 6 monthly intervals. All 82 patients in the study gained significant weight over time, this being greatest in the first 12 months, though continuing till 46 months. Serum triglycerides increased significantly as well. The limitations of the study included not being able to examine the role of risk factors such as ethnicity, family history or exercise (Kannabiran & Singh, 2008).
In a naturalistic study by Ganguli R et al (2001), changes in body weight and BMI in 100 patients treated for 4 months with risperidone or olanzapine were compared. There was no significant change in either measure in risperidone-treated patients. By contrast, patients receiving olanzapine showed a mean weight gain of approximately 2 kg from baseline, and a significant increase in BMI. Similarly, the proportion of patients in whom weight decreased or remained unchanged was 66% with risperidone, compared with 26% with olanzapine (Chue P, Cheung R, 2004).

In a 12 week-long prospective naturalistic observational study comparing risperidone (n=38), olanzapine (n=38) and clozapine in inpatients and outpatients, Strous R D et al (2006) observed that clozapine-treated patients showed significant increase in weight (6.9 ± 8%) compared to olanzapine (2.7 ± 3%) and risperidone (2.1 ± 6%). In a 12 week-long prospective observational study reported by Barnwal A et al (2012), 45 outpatients receiving typical and atypical antipsychotics were screened with varied psychiatric diagnosis. Of which 12 were withdrawn and 33 were followed up. At the end of the study, all the antipsychotics showed statistically significant weight changes (olanzapine +7.38 kg, risperidone -4.237 kg and haloperidol -5.538 kg). Among biochemical parameters, olanzapine was found to be associated with statistically significant increase in blood glucose, total cholesterol and triglycerides and decrease in HDL-C, whereas risperidone and haloperidol were associated with statistically significant increase in triglycerides.

In a 12 week-long prospective observational study reported by Barnwal A et al (2012), 45 outpatients receiving typical and atypical antipsychotics were screened with varied psychiatric diagnosis. Of which 12 were withdrawn and 33 were followed up. At the end of the study, all the antipsychotics showed statistically significant weight changes (olanzapine +7.38 kg, risperidone -4.237 kg and haloperidol -5.538 kg). Among biochemical parameters, olanzapine was found to be associated with statistically significant increase in blood glucose, total cholesterol and triglycerides and decrease in HDL-C, whereas risperidone and haloperidol were associated with statistically significant increase in triglycerides.

2.19.11. Effect of Atypical Antipsychotics on Glucose Dysregulation

Atypical antipsychotics were considered a significant breakthrough in the treatment of psychotic disorders, with low frequency or absence of extrapyramidal side-effects. Gradually case reports emerged which pointed to elevated levels of hyperglycaemia and diabetes mellitus associated with use of atypicals. (Kannabiran & Singh, 2008) There seems to be variability among the specific second-generation antipsychotics with respect to the incidence rates of diabetes (Llorente MD and Urrutia V, 2006)

Several mechanisms of glucose dysregulation have been proposed to explain this association. The medications most associated with diabetes are also those that induce the greatest amount of weight gain. There are patients who develop diabetes, however, in the absence of weight gain, so other causes must be sought. These drugs may disrupt hypothalamic regulation of glucose serum levels through hypothalamic dopamine antagonism. Additionally, elevated insulin levels have been found in 46% of clozapine-treated patients, compared with 21% of those receiving conventional medicines and 71% of a small sample of olanzapine-treated patients, suggesting that insulin resistance is a possible mechanism. Johnson et al (2005) found that in vitro low concentrations of olanzapine and clozapine (both potent muscarinic antagonists) inhibited cholinergics induced insulin secretion by blocking muscarinic M₃ receptor activity. Risperidone and ziprasidone had no such effects. These findings suggest an added role for potent anticholinergic activity as a contributing factor for development of diabetes. This is consistent with early findings of a higher association between low-potency conventional antipsychotics and increased weight gain. The low-potency drugs, in general, are much more anticholinergic than high-potency medications (Llorente MD and Urrutia V, 2006).

Melkersson and colleagues (2000) in studying patients on olanzapine for a median treatment period of 5 months, found elevated fasting glucose even in patients with normal BMI. This would suggest mechanism(s) other than being obese for the insulin resistance seen in these patients. At the same time, change in weight did have a positive correlation to overall blood glucose levels as would be expected.

Lifestyle changes and weight gain are among the possible factors to be associated with type 2 diabetes in addition to factors such as schizophrenia itself, its genetic factors and antipsychotic medication as reported by various comorbidity studies (Juvonen H et al, 2007).

2.19.13. Effects of Atypical Antipsychotics on Glucose Dysregulation - Studies:

Pre-clinical studies have indicated differences between antipsychotic in their response to insulin release. Best et al. (2005) studied the effects of clozapine and haloperidol on rat pancreatic β-cells in-vitro. The authors demonstrated the contrasting effects of clozapine and haloperidol on pancreatic β-cell function. Clozapine had no effect on β-cell membrane potential at fasting glucose levels but hyperpolarized the membrane potential, when glucose concentrations were high. In contrast haloperidol depolarized the membrane at both fasting and stimulatory levels of glucose. The effects of these two drugs on electrical activity only partially explained their effect on insulin release. Clozapine inhibited secretion of insulin in response to glucose, which could explain the hyperglycaemia and diabetes associated with it, but did not affect 'basal insulin release'. Interestingly, haloperidol had no effect on insulin release. (Kannabiran & Singh, 2008)
In a five year naturalistic study of 82 patients treated with clozapine (Henderson et al. 2000), 36.6% of patients developed diabetes, with 61.7% of the study population experiencing at least one episode of elevated fasting blood glucose. Serum triglycerides increased significantly as well. The limitations of the study included not being able to examine the role of risk factors such as ethnicity, family history or exercise. Koro et al. (2002a), in a large population-based, case-control study, found the risk of diabetes associated with antipsychotics to be quite variable. Olanzapine had 4.2 times the risk associated with conventional agents and 5.8 times the risk associated with no treatment. Risperidone had 1.6 times the risk of conventional drugs and 2.2 times the risk of no treatment.

Several large population retrospective studies have found that olanzapine and clozapine are associated with a significantly higher rate of diabetes than the conventional antipsychotics risperidone and quetiapine. The risk of diabetes, however, is higher with antipsychotic treatment use than in a general patient population sample (Llorente MD and Urrutia V, 2006).

Lindenmayer & Patel (1999) reported a case of olanzapine-induced diabetic ketoacidosis (DKA), which resolved following discontinuation of olanzapine treatment. The authors discuss the role of olanzapine in suppressing insulin release and in producing a hyperglycaemic response. Tovey et al. (2005) discuss two patients treated with clozapine, who subsequently developed diabetes mellitus, on routine blood testing. Blood sugar level returned to within the normal range after discontinuation of clozapine in one of the patients, but not in the other. The authors discuss the mechanisms by which clozapine may contribute to insulin resistance – by decreasing uptake of glucose in brain and peripheral tissue as well as by impaired β cell function. They stress the need for baseline measurements prior to and following initiation of treatment with clozapine.

Sernyak et al. (2002) used a national database to study the prevalence of diabetes mellitus in patients receiving atypical and typical antipsychotics over a 4 month period. As the study was cross-sectional in design, a causal relationship could not be explored. However, it was able to establish significant association between antipsychotic treatment and development of diabetes mellitus. Of the 38,632 patients included in the study, 58.6% were being treated with an atypical antipsychotic and 41.4% were being treated with conventional antipsychotics. To avoid the confounding effect of age, subjects were stratified according to age and results analysed. Nearly nine percent of subjects who were less than 60 years old and treated with atypical antipsychotic, had a diagnosis of diabetes mellitus. However, no significant association was detected at or above the age of 60. The authors suggest that patients who were vulnerable to developing diabetes would have developed the disease before this age, and those who were not vulnerable, would not develop it, in spite of antipsychotic use. There was no significant difference in the diagnosis of diabetes between those receiving atypical or conventional antipsychotics (nearly 19%), when compared across all age groups. 8.75%
of patients under the age of 40 receiving an atypical antipsychotic had diabetes mellitus compared to 6.43% of those treated with conventional antipsychotics ($\chi^2=7.24$, df=1, $p=0.007$). The odds of being diabetic was increased for clozapine, olanzapine and quetiapine but not for risperidone, when all age groups were considered. This difference disappeared in patients less than 40 years old, with all the 4 atypical antipsychotics being significantly associated with presence of diabetes mellitus.

Similarly, Lund et al (2001) found, when comparing patients treated with clozapine to those treated with typical antipsychotics, that in patients 20–34 years of age the incidence was ~5% in the clozapine group, versus 2% in the typical antipsychotics group, which made for a relative risk of 2.5 (Ferraioli et al., 2004).

Hagg et al (1976) when comparing clozapine to typical antipsychotics, found that the body weights of patients with impaired glucose tolerance or diabetes in the clozapine group were not higher than those with normal glucose metabolism. Henderson et al (2000) found that, over the 5-year study period, 67% of clozapine-treated patients had diabetes by the revised criteria of the Expert Committee, and that weight gain was not a significant risk factor for its development. However, they did find that patients on clozapine had significant weight gain and it continued for ~46 months in to the study period.

Newcomer et al. (2002) performed modified oral glucose tolerance tests in patients with schizophrenia, receiving clozapine, olanzapine, risperidone or typical antipsychotics. This study was conducted to determine if antipsychotics contributed to abnormalities in glucose regulation, independent of weight gain or abdominal adiposity. Forty eight patients with schizophrenia and 31 healthy adult controls participated in the study. Compared to subjects on conventional antipsychotics and healthy controls, patients on olanzapine and clozapine had elevated glucose levels at all time points following modified oral GTT (glucose tolerance test). Patients on Risperidone had a similar effect only when compared to untreated healthy controls. (cited by Kannabiran and Singh, 2008).

Melkerson et al (2000), in studying patients on olanzapine for a median treatment period of 5 months, found elevated fasting glucose even in patients with normal BMI. This would suggest mechanism(s) other than being obese for the insulin resistance seen in these patients. At the same time, change in weight did have a positive correlation to overall blood glucose levels as would be expected. In an earlier study, comparing clozapine with the typical antipsychotics, Melkerson et al (1999) found no significant difference in BMI between the two groups, yet more patients in the clozapine group had elevated insulin levels compared to the typicals group (46% versus 21%).

In studying both clozapine and olanzapine associated diabetes, Koller et al (2001) and Koller and Doraiswamy (2002) found that the time to onset of diabetes or hyperglycemia varied greatly among patients,
from immediately after one dose to > 5 years with clozapine, and from 2 days to 45 months with olanzapine. Of the patients who developed glucoregulatory problems, the majority of cases occurred within 6 months of initiation of treatment, and 27% and 18%, respectively, were diagnosed with diabetes within the first month of treatment with clozapine and olanzapine. Furthermore, 63% of cases of primarily new onset diabetes with blood glucose >700 mg/dL occurred within 3 months of the start of clozapine therapy, with comparable numbers for olanzapine. The variable time to onset of problems, very early in many cases (i.e. before weight gain) and years later in others, as well as the severity of these problems along that time range, point to a multifactorial mechanism or perhaps multiple separate mechanisms towards the onset of glucoregulatory problems associated with these drugs.

Mackin and colleagues (2005) hypothesized that atypical antipsychotics were associated with increased metabolic abnormality compared to conventional antipsychotics. They undertook a cross-sectional study of 106 patients, with the only inclusion criterion being treatment with antipsychotic medication for a minimum of 6 months. All 12 patients (11.6%) receiving atypical antipsychotic had a ‘glucose homeostasis’ disorder.

Olanzapine compared to risperidone in a large population based nested case-control study was found to be associated with a significant risk of diabetes. Koro et al. (2002) studied data (between 1987 and 2000) from 3.5 million patients on the United Kingdom based General Practice Research Database. Of the 19,637 patients with schizophrenia, who were eligible for study purposes, 451 developed diabetes during a mean follow up of around 5 years. The risk of developing diabetes was non-significant with the use of risperidone (odds ratio = 1.6, p = 0.160), slightly increased with conventional antipsychotics (odds ratio = 1.3, p = 0.013) and significantly increased with the use of olanzapine (odds ratio = 4.4, p = 0.002).

**Fig. 30. Distribution of glucose intolerance reactions among atypical antipsychotics**
(Ref Hedenmalm K et al., 2002)
The WHO Collaborating Centre for International Drug Monitoring receives summary clinical reports of individual adverse drug reactions from the national centres in 63 countries around the world. Reports were identified for clozapine, olanzapine and risperidone in the WHO database. From its start in 1968 until December 2000, the WHO Collaborating Centre received 868 reports of glucose intolerance with clozapine (n = 480), olanzapine (n = 253), and risperidone (n = 138). The strengths of the associations over time between the atypical agents clozapine, olanzapine or risperidone and glucose intolerance are presented in the given figure. In conclusion, clozapine, olanzapine and risperidone were significantly found to be associated with glucose intolerance. Authors identified the following risk factors for glucose intolerance: an underlying diabetic condition, an increase in weight, male gender, and concomitant use of valproic acid, selective serotonin reuptake inhibitors, or buspirone (Hedenmalm K et al., 2002).

In a 12 week-long prospective naturalistic observational study comparing risperidone (n=38), olanzapine (n=38) and clozapine in inpatients and outpatients, Strous R D et al (2006) observed that patients treated with clozapine showed greater increase compared to other drugs with respect to glucose ($\chi^2=5.99$, df=2, $p=0.05$). The risk of pathological change of glucose was associated with gender, with females showing greater pathological change (32.6%) compared to males (13.2%). However, no association between drug and glucose increase was found within male or female patients.

An Indian observational study conducted by Umadevi P and Murugam S (2009) to focus on metabolic disturbances which comprehensively examined metabolic parameters viz. weight/BMI, serum glucose and serum lipids together, conducted in 60 schizophrenic in-patients of age group 18-65 years of both sexes. It reported increase in blood glucose levels in schizophrenic patients treated with antipsychotic drugs. However, it was hospital based study consisting in-patients belonging to good socioeconomic background.

In a randomized open-label study of 12 weeks of patients with schizophrenia (DSM-IV diagnosis), Ingole S et al, 2009, observed that mean body weight and BMI were significantly increased from baseline to 6 and 12 weeks in both olanzapine (n=30) and risperidone groups (n=30) ($P<0.001$). The mean blood sugar was found to be significantly elevated after 6 and 12 weeks of treatment with olanzapine ($P<0.001$) but not in risperidone group. However, regardless of statistically significant changes in FBG by olanzapine at the study endpoint, they were still within clinically normal range [104.73 (SD 1.850)] (below 126 mg/dL).

In a 12 week-long observational study reported by Barnwal A. et al (2012), 45 outpatients receiving typical and atypical antipsychotics were screened with varied psychiatric diagnosis. Of which 12 were withdrawn and 33 were followed up. At the end of the study, regardless of statistically significant changes found in FBG at the study endpoint, they were still within clinically normal range [86.21 (SD 3.19)] (below 126 mg/dL).
2.19.14. Effects of Atypical Antipsychotics on Lipid Profile (Dyslipidemia or Hyperlipidemia)

Dyslipidaemia is an important component of the metabolic syndrome, which occurs along with glucose dysregulation and weight gain in patients treated with atypical antipsychotics (Kannabiran & Singh, 2008). Hyperlipidemia (increased triglycerides and cholesterol) tends to parallel weight gain. Its propensity among atypical antipsychotics as follows: (Tandon and Jibson, 2003)

clozapine > olanzapine > quetiapine ≥ risperidone > ziprasidone = aripiprazole

Because several of the newer antipsychotics are associated with significant weight gain, one would expect that hyperlipidemia should also be associated with the use of these medications.

a) Pathogenesis of Dyslipidemia by Antipsychotics

Dyslipidaemia is characterised by increased FFAs, elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, increased small, dense low-density lipoprotein (LDL) cholesterol and increased apolipoprotein B. The high prevalence of hyperlipidaemia in the general population and the heterogeneity in the definition of hyperlipidaemia make conclusions about changes of lipid metabolism of psychiatric patients during therapy with psychotropic drugs difficult. Additionally to weight gain and diabetes, some SGAs cause hypertriglyceridaemia, which is an independent risk factor of coronary arteriosclerosis. (Tschoner A et al., 2007)

Increased adiposity can result in excess FFA release from hypertrophic adipocytes leading to higher FFA concentrations. These can induce muscle and hepatic insulin resistance, endothelial- and pancreatic-cell dysfunction and increased VLDL triglyceride production (See figure). (Tschoner A et al., 2007)

Fig. 31. Pathophysiology of Obesity-induced Dyslipidaemia (Ref.: Tschoner A et al., 2007)

Figure Pathophysiology of obesity-induced dyslipidaemia. Visceral obesity and a decreased effect of insulin on adipose tissue resulting in reduced inhibition of HSL lead to an excess release of FFAs. In the liver, FFAs are synthesised to triglyceride-rich VLDL. CETP mediates the transfer of cholesteryl esters from cholesteryl ester-rich lipoproteins to TG-ricl lipoproteins in exchange for TGs. HDL and LDL particle size is further decreased by HL-mediated loss of TGs. FFA, free fatty acid; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; CETP, cholesteryl ester transfer protein; HSL, hormone-sensitive lipase; HL, hepatic lipase.
b) Dyslipidemia by Antipsychotics – Studies

It has been shown in studies by Melkersson and colleagues (1999, 2000) that atypical antipsychotics such as clozapine and olanzapine may cause both insulin resistance as well as increased insulin secretion. The authors found that glucose levels remained high in the face of hyperinsulinemia, indicating insulin resistance, but they also found something else. These patients also showed low insulin-like growth factor binding protein-1 (IGFBP-1 levels [produced in the liver by an insulin regulated process]), at fasting insulin levels that were within normal limits. Since IGFBP-1 usually has an inverse correlation to insulin levels in healthy subjects, its high levels instead can be expected. As they point out, this makes sense if a high diurnal insulin secretion over a 24-hour period is considered rather than just the low simple fasting insulin levels. In fact it is known that diurnal insulin secretion is reflected by IGFBP-1 better than by fasting morning insulin levels. This would lead to the possibility of either a direct or indirect effect of olanzapine and clozapine on the pancreatic beta cells, causing increased secretion of insulin. (Ferraioli et al, 2004)

A prospective study by Wu RR et al (2006) comparing the effects of the SGAs clozapine, olanzapine, risperidone and the FGA sulpiride on glucose and lipid metabolism in first-episode schizophrenia at baseline and 8 weeks after inclusion showed that besides higher C-peptide, fasting insulin and insulin resistance index (IRI), cholesterol and triglyceride levels were significantly increased in the clozapine and olanzapine groups. Because of these results the authors recommend that baseline and 6-month monitoring of fasting blood glucose, fasting cholesterol and triglyceride levels should be obtained in routine clinical practice with all antipsychotics to monitor the risk for development of hyperglycaemia and hypercholesterolaemia (Tschoner A et al, 2007).

In a comparative study by Wirshing DA et al (2002), treatment with various antipsychotics resulted in significantly elevated 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 HDL cholesterol during treatment with clozapine and olanzapine, whereas total cholesterol levels were significantly lower in risperidone- and fluphenazine-treated patients.

A large retrospective case-control study from the United Kingdom by Koro et al (2002b) assessed the effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in 18,309 patients with schizophrenia. Olanzapine users had a significantly increased risk of hyperlipidemia compared with patients receiving typical antipsychotics (3.36-fold increase in risk) or no antipsychotic exposure (4.6-fold increase in risk). In contrast, risperidone was not associated with an increased risk of hyperlipidemia compared with typical antipsychotics or no exposure. In a study by Brown and Estoup (2005) described a negative effect of olanzapine administration on total cholesterol and triglycerides, whereas favourable metabolic effects were observed in
ziprasidone-treated patients with regard to total cholesterol, LDL and HDL. These results were confirmed in another study with 1493 patients by Lieberman JA et al, 2005.

An increase of serum lipid levels was already seen after 4 weeks of treatment with olanzapine or clozapine and was significantly correlated with increasing BMI. As amisulpride and ziprasidone had no significant effect on serum lipid levels, the authors suggest these drugs as a favourable alternative treatment for already overweight patients (Rettenbacher MA et al, 2006).

Case series have played an important role in highlighting the increased prevalence of hyperlipidemia associated with atypical antipsychotic use. A retrospective case series by Meyer (2001) consisted of 14 psychiatric patients, treated with olanzapine or quetiapine, referred for treatment of severe hypertriglyceridemia (defined as fasting triglycerides > 600 mg/dL). On average, it took 9 months for the triglyceride levels to peak. The mean peak triglyceride levels following treatment with atypical antipsychotics was 1459.14 mg/dL from a mean baseline of 211.29 mg/dL. Though BMI and weight increased for all patients from that at baseline, hyperlipidemia was not correlated with weight gain, change in BMI, use of lithium or valproate or previous history of hyperlipidemia. The author discusses regarding the increased risk of pancreatitis and cardiovascular events, especially with triglyceride levels above 1000 mg/dL (Kannabiran & Singh, 2008).

In a five year naturalistic study of 82 patients treated with clozapine (Henderson et al. 2000), 36.6% of patients developed diabetes, with 61.7% of the study population experiencing at least one episode of elevated fasting blood glucose. Serum triglycerides increased significantly as well. The limitations of the study included not being able to examine the role of risk factors such as ethnicity, family history or exercise.

Saari et al (2004) suggested that the pathogenesis of hyperlipidemia is related to weight gain, with accumulation of abdominal fat increase release of free fatty acids in the liver and accelerating hepatic triglyceride synthesis as well as very low density lipoprotein (VLDL) release. They further suggested that increased lipids impair glucose metabolism, leading to hyperglycaemia and Type 2 DM (Kannabiran & Singh, 2008).

Osser and others (1999) evaluated the effects of olanzapine on weight, fasting total cholesterol, and triglycerides in 25 patients with schizophrenia and related psychosis. After 12 weeks of olanzapine treatment, the group mean body weight increased 5.4 kg (P < 0.02). Although there was no significant change in cholesterol levels, the mean triglyceride levels rose by 37%.
Severe hypertriglyceridemia (>600 mg/dL) without associated elevations in total cholesterol has been described in uncontrolled observations of patients treated with olanzapine or quetiapine. A chart review of 215 patients treated with clozapine, olanzapine, risperidone, quetiapine, haloperidol, or fluphenazine reported significantly greater increases in mean triglyceride levels in patients receiving clozapine or olanzapine compared with those receiving other antipsychotics. Clinically meaningful elevations in triglyceride levels (triglycerides >200 mg/dL) developed in 56% of clozapine-treated patients, 40% of quetiapine-treated patients, 39% of olanzapine-treated patients, and 31% of those receiving risperidone. Another retrospective chart review found that olanzapine is associated with significantly greater mean increases in triglycerides and cholesterol than risperidone in patients <60 years of age (Newcomer JW, 2005).

Data from clinical studies suggest that olanzapine and quetiapine may increase triglyceride levels in patients with schizophrenia, although data on quetiapine are limited. A randomized, open-label, parallel-group study in patients with schizophrenia evaluated the effects of ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, and haloperidol on fasting lipids over 15–25 days of treatment. Ziprasidone and haloperidol produced statistically significant reductions from baseline in total cholesterol and triglycerides. Of note, short-term treatment with ziprasidone resulted in a 28% reduction in triglyceride levels. Statistically significant increases in plasma triglycerides were observed with both olanzapine (31% increase from baseline) and quetiapine (18% increase from baseline). No statistically significant changes in triglycerides or cholesterol levels were seen with risperidone. Thioridazine did not significantly affect triglyceride levels, but increased total cholesterol (Newcomer JW, 2005).

The 6-week, randomized, double-blind study by Simpson and colleagues (2004) examined the effects of ziprasidone and olanzapine on lipid profiles. Olanzapine produced statistically significant increases from baseline in total cholesterol (median change 19.5 mg/dL), low-density lipoprotein (LDL) cholesterol (median change, 13.0 mg/dL), and triglycerides (median change 26.0 mg/dL). Ziprasidone was associated with small, nonsignificant decreases in total cholesterol, LDL cholesterol, and triglycerides. Differences between groups were highly significant for all three measures. A 26-week study comparing aripiprazole with olanzapine demonstrated that aripiprazole does not produce any clinically significant changes in triglyceride or cholesterol levels. Together, findings from clinical studies indicate that treatment with ziprasidone and aripiprazole does not adversely affect lipid profiles and may even improve triglyceride and cholesterol levels in some patients who have previously been treated with other agents. (Newcomer JW, 2005)

Another theme of interest is the possible association between glucose dysregulation and hyperlipidemia in patients taking atypical antipsychotics. Several studies have demonstrated hyperlipidemia, especially hypertriglyceridemia, in patients who also showed glucose dysregulation during treatment with clozapine.
and olanzapine. Furthermore, hyperlipidemia, and especially hypertriglyceridemia, may itself be associated
with insulin resistance (and secondary increased insulin secretion) (Ferraioli et al., 2004)

In both of the previously mentioned Melkersson and colleagues studies, which considered clozapine and
olanzapine, respectively, patients on both of these medications demonstrated elevated insulin levels (71% of
the patients in the olanzapine study and 46% in the clozapine study). Lipids were measured as part of the
olanzapine study and it was found that 85% of patients had hypercholesterolemia and 62% had
hypertriglyceridemia. Still not clear then is the nature of the relationship between hyperlipidemia and insulin
resistance (i.e. whether it is one of causality or whether these adverse effects are independent of one
another, or maybe “relatively independent”) (Ferraioli et al., 2004)

Murashita M et al (2007) in a naturalistic study in 15 stable schizophrenic patients on chronic risperidone
monotherapy compared with 25 healthy controls examined the effect of risperidone on fasting blood
glucose, insulin, HbA1c, growth hormone, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol,
leptin, total ghrelin, active ghrelin and prolactin in addition to body weight, BMI, body fat percentage, clinical
symptomatology, global functioning and quality of life. There were statistically significant changes found at
biochemical level with respect to FBG, triglycerides, HDL-cholesterol, leptin, total ghrelin, active ghrelin and
prolactin (all p < 0.05). There were near significant changes in case of LDL-cholesterol (p = 0.0513) Also there
was significant change in BMI and body fat percentage. The mean dose of risperidone used (2.6 ± 1.1
mg/day, range 1-5 mg/day) in stable schizophrenics was lower than used in our present study (4.76 ± 1.5
mg/day, range 1-8 mg/day used at endpoint)

Amaladoss, Balram and Wang (2009) in a randomized study of 1 year in 121 patients (119 completed the
study) to determine the treatment effects of atypical antipsychotics on triglycerides, found mean triglyceride
levels in males were higher in risperidone compared with olanzapine (1.92 > 1.7), whereas in females were
higher in olanzapine compared with risperidone (1.97 > 1.7).

Smith RC et al (2010) in a randomized 5-month study in 46 in-patients to examine the effects of olanzapine
and risperidone on lipid metabolism in chronic schizophrenic patients with long-term antipsychotic
treatment found that overall, there were no differential drug effects on any fasting lipid measure and fasting
triglycerides did not increase in olanzapine treated patients after 5 months of treatment. However, at 2
months of drug treatment the fatty meal test (FMT) revealed a significantly greater increase in triglycerides,
and very low density (VLDL) cholesterol and triglycerides, in olanzapine compared to risperidone patients
(Ps=.05-01) There was no difference between olanzapine vs. risperidone on development of metabolic
syndrome during the 5 month treatment period. He concluded that chronic schizophrenic patients treated
for years with first-generation (typical) and second-generation (atypical) antipsychotics may have developed
tolerance to the effects of olanzapine on increasing fasting triglycerides and other lipids, but some underlying metabolic abnormalities may be revealed in postprandial tests of lipid metabolism. These findings suggest that the development of standardized tests and criteria for measurement of postprandial triglycerides and related lipid levels, in addition to fasting levels, may be helpful in identifying metabolic effects of olanzapine and other atypical antipsychotics in chronically treated schizophrenics.

In a 12-week-long prospective naturalistic observational study comparing risperidone (n=38), olanzapine (n=38) and clozapine (n=55) in inpatients and outpatients, Strous R D et al (2006) observed that treated with clozapine showed greater pathological change compared to other drugs with respect to triglycerides ($\chi^2=9.57, \text{df}=2, p=0.008$). Risperidone patients tended to exhibit reduced cholesterol levels. However, no significant difference between the medications was noted with respect to cholesterol.

There are two Indian observational studies that focus on metabolic disturbances. Umadevi and Murugam (2009) examined metabolic parameters viz. weight/BMI, serum glucose and serum lipids in 60 schizophrenic in-patients of age group 18-65 years of both sexes. Increased total cholesterol and triglycerides levels have been reported in schizophrenic patients treated with antipsychotic drugs. However, it was a hospital-based study consisting of patients belonging to good socioeconomic background. In a 12-week-long observational study reported by Bamwal A et al (2012), 45 outpatients receiving typical and atypical antipsychotics were screened with varied psychiatric diagnosis. Of which 12 were withdrawn and 33 were followed up. At the end of the study, among biochemical parameters, olanzapine was found to be associated with statistically significant increase in total cholesterol and triglycerides and decrease in HDL-C, whereas risperidone and haloperidol were associated with statistically significant increase in triglycerides.
Thus antipsychotic drugs have a profound effect on metabolism, being able to cause hyperglycaemia, dyslipidaemia and obesity. These metabolic side-effects contribute substantially, in synergism with lifestyle factors and difficult access to health care, to the very high cardiovascular risk and reduced life expectancy of patients with severe mental illness. Moreover, antipsychotic-related metabolic disorders occur in psychiatric patients of any age, being particularly severe in children and adolescents (Morteimer A, McKenna P., 2010). The non-neurological side effects of antipsychotic medications received less attention prior to the introduction of the atypical antipsychotic medications (Hansen TE et al., 2004).

The impact of antipsychotic drugs on metabolic parameters varies widely according to individual drugs. Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine appear to have intermediate effects. Aripiprazole and ziprasidone are associated with little or no significant weight gain, diabetes, or dyslipidemia, although they have not been used as extensively as the other agents. (ADA-APA-AACE-NAASO, 2004)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight gain</th>
<th>Risk for diabetes</th>
<th>Worsening lipid profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Ziprasidone</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* = increase effect; - = no effect; D = discrepant results. 'Newer drugs with limited long-term data.
The choice of SGA for a specific patient depends on many factors. The likelihood of developing severe metabolic disease should also be an important consideration. When prescribing an SGA, a commitment to baseline screening and follow-up monitoring is essential in order to mitigate the likelihood of developing CVD, diabetes, or other diabetes complications. (ADA-APA-AACE-NAASO, 2004)

Metabolic side-effects of antipsychotics such as weight gain, diabetes and dyslipidaemia can explain in part the high cardiovascular morbidity and mortality of psychiatric patients. Despite numerous published guidelines, most metabolic side-effects remain undiagnosed and untreated. Potentially effective prevention and treatment strategies are available, together with a simple screening protocol. Further research in this area, and the implementation of currently available clinical evidence, could help to improve the health of patients with severe mental illness. (Morteimer A, McKenna P., 2010)

2.20.1. Generic Monitoring Protocol for Patients on Atypical Antipsychotics

Patients on atypical antipsychotics should be screened and monitored for metabolic parameters as part of routine psychiatric assessments.

Table 17. Monitoring Guideline: American Diabetes Association and American Psychiatric Association, 2004

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>Quarterly</th>
<th>Annually</th>
<th>Every 5 years</th>
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<tbody>
<tr>
<td>Personal/family history</td>
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<td></td>
<td></td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td>Weight (BMI)</td>
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<tr>
<td>Fasting plasma glucose</td>
<td>+</td>
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<td>Fasting lipid profile</td>
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One of the most often cited published guidelines is the ADA/APA guidelines (ADA-APA-AACE-NAASO, 2004), which has a broad medical representation and a practical monitoring structure useful to clinicians that fulfills most of the established monitoring goals. (Gill JS et al., 2012) In November 2003, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity convened a consensus development conference on the subject of antipsychotic medications and diabetes and obesity. ADA-APA-AACE-NAASO (2004) consensus statement (commonly known as ADA/APA consensus guidelines) has recommended stringent monitoring of metabolic status and cardiovascular risk factors in psychiatric patients receiving antipsychotic medications. The statement recommends baseline screening measures at the initiation of any antipsychotic medication.
These measures include weight and height to calculate body mass index (BMI), waist circumference, blood pressure, fasting plasma glucose, fasting lipid profile, and personal and family history of metabolic disorders. By completing this assessment, it can be determined if the patient is overweight (BMI 25.0-29.9) or obese (BMI >30), has prediabetes (fasting plasma glucose 120-125 mg/dL) or diabetes (fasting plasma glucose >126 mg/dL), hypertension (blood pressure >140/90 mmHg), or dyslipidemia. If one or more of these disorders are present, the panel recommends initiation of treatment. (ADA-APA-AACE-NAASO, 2004)

The panel also recommends nutritional and physical-activity counseling for all patients who are overweight or obese, especially if an atypical agent will be initiated. Particular importance is placed on the education of patients, caregivers, and family members on signs and symptoms of diabetes and also on the possible metabolic adverse effects associated with atypical agents. (ADA-APA-AACE-NAASO, 2004)

Baseline screening measures should be followed by ongoing monitoring. Reassessment of all measures, except personal and family history and waist circumference, is recommended after 12 weeks of treatment for all patients treated with atypical antipsychotic medications. Thereafter, fasting plasma glucose, blood pressure, and waist circumference assessments should be completed annually and fasting lipid profile measured every 5 years. Weight should be followed monthly for the first three months and quarterly thereafter. The panel recommends switching to an agent with less deleterious effects on metabolic functions if a patient experiences a 5% increase in body weight and/or worsening glycemia or dyslipidemia at any time during therapy. This should be done through cross titration and gradual discontinuation of the current medication. The initial dosage and escalation strategy of the new agent depend on the individual profiles of each medication. Along with altering the treatment, the panel recommends dietary restriction, exercise, and behavior modification. (ADA-APA-AACE-NAASO, 2004)

Small, short-term studies have reported this approach to be successful in managing patients with weight gain. Pharmacologic interventions to reduce weight gain have not been found to be dependably effective in patients receiving atypical antipsychotics and should be discouraged. (Tahir R, 2007)
2.20.2. Adherence to Metabolic Monitoring Guidelines in Atypical Antipsychotic-treated Subjects: Do physicians comply?

Although the majority of clinicians correctly identified possible metabolic side effects associated with atypical antipsychotic medications, a significant proportion of clinicians did not identify weight gain (14.7%), glucose dysregulation (14.7%), dyslipidemia (34.3%) and pancreatitis (100%). In terms of screening parameters, a large proportion of clinicians failed to identify BMI (25%), waist circumference (56.2%), lipids (27.1%), glucose (29.2%), and blood pressure (87.5%) as parameters that need to be measured at baseline. Similar percentages of clinicians failed
to identify these screening parameters for monitoring purposes. There was a significant lack of consensus among clinicians about who should be responsible for measuring and following metabolic parameters.

It was concluded by Rieu-Werden ML et al. (2011) that gaps exist in prescribing clinicians' awareness of side effects and risks associated with antipsychotic medications, and in their familiarity with established metabolic monitoring guidelines and screening parameters. Knowledge gaps regarding monitoring guidelines could be due to lack of awareness of guidelines, confusion over which set of monitoring guidelines to follow, or confusion regarding who is responsible for performing these measurements. Further research is necessary to determine the exact cause of these knowledge gaps. This gap analysis can be used to design and evaluate focused educational interventions targeted to remediate these knowledge gaps.

Gill JS et al. (2012) in their retrospective observational study in 405 patients treated at University Malaya Medical Centre (UMMC) a tertiary referral centre located in Kuala Lumpur were found to have been newly started on AA after June 2005 who underwent the required assessments at baseline, first month, second month, third month and at one year in accordance to the recommended ADA-APA Guidelines, 2004. In summary, the overall rate of metabolic parameters monitoring in patients prescribed with AA drugs in UMMC was low. This concurs with the results of previous studies (Gul et al., 2006, Mackin et al., 2007; Motsinger et al., 2006, Taylor et al., 2004). There are several possible reasons why compliance metabolic monitoring in patients on AA treatment is poor (Gill JS et al., 2012). Medical care for patients with severe mental illness has frequently been marginalized due to the limited resources in medical care, especially in non-developed countries. Besides the belief that there is a lack of time and shortage of staff to perform these procedures, little medical knowledge or emphasis on medical needs in mental health settings form barriers to the implementation of published monitoring guidelines (Cohn and Sernyak, 2006).

Meanwhile, the issue of who is responsible for monitoring metabolic abnormalities in patients receiving AA drugs is much debated. Cohn and Sernyak (2006) suggested that the responsibility for monitoring metabolic abnormalities in patients prescribed with AA should come along with the prescription. They claimed that it is not necessary for psychiatrists to actually perform the monitoring tests. However, they are responsible to ensure that the task is clearly delegated if they are not going to perform the tests. The issue of liability also acts as a barrier to monitoring guidelines implementation. Some clinicians are concerned about the types of added liability are implied when monitoring tests are performed that would document the significant metabolic abnormalities such as diabetes or dyslipidemia. Patient-related issues such as persisting symptoms such as paranoia and mania; cognitive deficits; access and affordability to medical care and non-adherence to treatment recommendations can also be barriers to implement monitoring guidelines. Furthermore, some clinicians are resistant to change and there is a lack of familiarity with monitoring guidelines which makes the
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monitoring guidelines difficult to implement (Narasimhan and Bailey, 2008). Some studies also suggest that some of the psychiatrists are ignorant of metabolic dysfunctions associated with AA drugs (Gul et al., 2006; Mackin et al., 2007) [Cited by Gill JS et al, 2012].

Weissman et al. (2012) carried out a retrospective analysis conducted using administrative data extracted from local databases at four sites in the Veterans Administration (VA) New York/New Jersey VISN 3 Healthcare Network. The study population included individuals under age 65 who were treated for schizophrenia or schizoaffective disorder diagnosed at two or more mental health visits and who started a “new” SGA treatment during the study period. Of 4,468 individuals who met our diagnostic criteria, 4,194 received antipsychotic treatment during the observation period. Of these, 1,955 received only one antipsychotic during the study and 2,239 received treatment with 2 or more different agents. 1,626 individuals met all criteria for inclusion in the study population.

The authors concluded that monitoring rates for total cholesterol and weight were low prior to the introduction of monitoring guidelines for treatment with SGAs, even in a healthcare system where psychiatric and medical care are integrated and recorded in a single medical record. Initiating SGA treatment did not appear to trigger monitoring above and beyond rates observed in routine clinical practice. However, lipid monitoring rates were higher in the VA compared to studies conducted in non-integrated health systems. Diagnoses related to metabolic issues—diabetes and hyperlipidemia—were the strongest predictors of monitoring. (Weissman E et al. 2012).

Studies examining the impact of monitoring guidelines have been disappointing so far. In addition to the clinical characteristics authors examined, it is suggested that future studies should analyze provider characteristics, patient characteristics not recorded in administrative data (e.g., assertiveness, knowledge, attitudes toward medical treatment), or other environmental characteristics such as family involvement that might affect monitoring rates. Identifying factors that predict metabolic monitoring could potentially provide clues to improving other aspects of clinical care. Finally, public mental health authorities can summarize administrative data to generate benchmarks prior to policy changes and monitor practice following the initiation of such policies (Weissman E et al. 2012).

Gumber R et al (2010) carried out an audit on data between May 2006 and December 2007, involving 69 patients with schizophrenia receiving atypical antipsychotics on the clinic register of the Charnwood metabolic clinic recording monitoring of metabolic side effects of atypical antipsychotics on a standard form (proforma) at each visit. The re-audit was carried out on data between December 2007 and January 2009, involving 123 patients with schizophrenia receiving atypical antipsychotics on the clinic register. The audit resulted in a 24% increase in the number of patients on atypical antipsychotics being referred to the metabolic clinic. The number of abnormal results communicated to primary care showed a significant
improvement of 25% (P = 0.001), and ultimately the number of patients who received intervention improved by 17% (P < 0.001). In the re-audit, consultants' referral rates were improved at 67%, albeit still well below the audit standard. This reflects the limited capacity of the metabolic clinic and it is possible that only high-risk patients are being referred.

Despite implementation of audit recommendations, high-density lipoprotein and glucose tests were insufficiently requested by specialty trainees and the number of glucose results not completed in fact increased. Although the reason behind this is unclear, this does indicate the need for further education of specialty trainees and clarity on blood test forms. Clinical implications of the audit feedback has been effective in changing clinical practice. The audit demonstrated the potential value of a metabolic clinic and shared care between primary and secondary practitioners for this group of high-risk patients (Gumber R et al., 2010).

The authors have stated that the metabolic profile of patients on atypical antipsychotics is clearly of concern. Psychiatrists and GPs (general practitioners) must work together to carry out efficient monitoring of all relevant parameters so that early interventions to reduce the risk of cardiovascular disease and type 2 diabetes are possible. However, in response to this audit and its clinical implications stated by Gumber R et al (2010), in his letter Paul G Reed (2010) states that his critical review of the evidence of risk to patients with mental illness does not support the use of such widespread monitoring (Gumber R et al, 2010).

Reed (2010) has used the example of lipid monitoring to illustrate this. A large general practice study in the UK found that the relative risk of death from cardiovascular disease in people with mental illness when compared with controls was highest in younger people and reduced with age to a point that was not statistically significant in people over the age of 75. The authors of that study claim that the three-fold increase in deaths for people under the age of 50 is the most worrying. This may be so, but the finding is worthy of closer scrutiny, especially when the implications for screening are being considered. In fact, the absolute risk of death from coronary heart disease in people with mental illness aged 18-49 was 0.1% over a median follow-up period of 4.7 years.

It was suggested by Gill JS et al (2012) that instead of recommending guidelines, which serves only as "guides", standardized operating procedures (SOP) regarding metabolic monitoring be implemented, compelling doctors to adhere to the monitoring schedule. This ultimately is for the benefit of our patients and to safeguard their well being. (Gill JS et al, 2012)

However, Reed (2010) states that the European guidelines for prevention of heart disease recommend monitoring of lipids only when the 10-year risk reaches 5% or more. It would seem difficult therefore to justify routine monitoring of mentally ill people aged 18-49. Also of concern is the lack of evaluation of harm to patients caused by what is essentially a screening programme of high-risk individuals.
Such programmes are known to be associated with harm in a variety of forms. These include overdiagnosis, overtreatment and anxiety concerning the illness being investigated. Reed lastly suggests that for a patient to give informed consent to participate in this kind of programme, they should be informed of the uncertainties inherent in it and the likelihood or otherwise of benefit to them of such a screening. It is time to take stock and critically review which, if any, of these investigations are necessary for our patients.

Thus there is a cautious need of considering and implementing the metabolic monitoring guidelines based on regional (local) - ethnicity, cultural characteristics, healthcare infrastructure, clinicians' prescribing pattern of antipsychotics, knowledge and awareness as well as defined responsibilities of the concerned healthcare staff and the need of the individual patient.