EFFECT OF METFORMIN ON WEIGHT GAIN INDUCED BY OLANZAPINE

BY

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Dissertation submitted to the

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In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE
IN
PHARMACOLOGY

Under the guidance of

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April 2015

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I hereby declare that this dissertation entitled **"EFFECT OF METFORMIN ON WEIGHT GAIN INDUCED BY OLANZAPINE"** is a bonafide and genuine research work carried out by me under the direct guidance of **Dr. SARALA. N, MD** Professor and HOD, Department of Pharmacology Sri Devaraj Urs Medical College, Tamaka, Kolar.

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This is to certify that, the ethics committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has unanimously approved the dissertation work of **Dr. CHETAN KUMAR. G**, a postgraduate student in the Department of Pharmacology of Sri Devaraj Urs Medical College entitled "**EFFECT OF METFORMIN ON WEIGHT GAIN INDUCED BY OLANZAPINE"** to be submitted to the Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar.

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In the end I thank ***The Almighty*** for blessing me and giving me the strength and courage to complete this task.

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Place: Kolar **Dr. CHETAN KUMAR. G**

Dedicated with

REVERENCE

to

My Parents

LIST OF ABBREVIATIONS

5-HT	Serotonin
AMPK	Adenosine monophosphate – activated protein kinase
ANOVA	Analysis of variance
BMI	Body mass index
DSM	Diagnostic and statistical manual of mental disorders
ECT	Electroconvulsive therapy
EPS	Extrapyramidal symptoms
FDA	Food and drug administration
FBS	Fasting blood sugar
GABA	gamma-Aminobutyric acid
HbA_{1c}	Glycated hemoglobin
ICD	International statistical classification of diseases and related health problem
LSD	Lysergic acid diethylamide
NMDA	N-methyl-D-aspartate
PET	Positron emission tomography
RDC	Research diagnostic criteria
SGAs	Second generation antipsychotics
SHBG	Steroid hormone binding globulin
WHO	World health organization

ABSTRACT

INTRODUCTION:

Olanzapine is an atypical antipsychotic used in schizophrenia and bipolar affective disorder, but it is associated with weight gain and metabolic syndrome. Metformin is known to decrease insulin resistance and abnormal glucose metabolism. Therefore metformin might prove useful in preventing weight gain induced by olanzapine.

OBJECTIVES:

To study the effect of metformin on body weight, body mass index, waist circumference, hip circumference, waist to hip ratio, blood glucose levels in patients receiving olanzapine and to observe the adverse effects of olanzapine and metformin

MATERIALS AND METHODS:

Sixty five patients with schizophrenia and bipolar mania were randomly assigned to treatment for 12weeks with olanzapine 10mg/day, plus metformin 850mg/day (n=33) or olanzapine alone (n=32). Body weight, body mass index, waist circumference, hip circumference and waist to hip ratio were measured at baseline, weeks 4, 8 and 12. Fasting plasma glucose was estimated at baseline and end of the study.

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RESULTS:

59/65 (90.8%) patients completed the 12weeks study period. The body weight, body mass index, waist circumference, hip circumference and waist to hip ratio increased in both groups but it was less in patients receiving metformin along with olanzapine. More than 7% weight gain was observed only in 43.3% receiving olanzapine plus metformin but it was 86.2% with olanzapine alone which was significant (p=0.001). Fasting plasma glucose had decreased significantly in olanzapine plus metformin group at week12.

CONCLUSION:

Although addition of metformin did not show a substantial change in weight, it is likely that a higher dose or longer duration of therapy may be required to observe such effects.

Key words: Atypical antipsychotics, Metformin, Weight gain

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Introduction

INTRODUCTION

Schizophrenia is a severe form of mental illness affecting about 7 per thousand of the adult population, mostly in the age group 15-35 years. Though the incidence is low (3/10,000), the prevalence is high due to chronicity.[1] Its clinical features are Positive symptoms: delusion, hallucinations, thought disorders, catatonia, abnormal and disorganized behavior. Negative symptoms: withdrawal from social contacts, flattening of emotional responses, anhedonia, reluctance to perform everyday tasks.[2]

Atypical or second generation antipsychotics (SGA) drugs such as aripiprazole, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, amisulpride, zotepine and sertindole are more commonly used than typical antipsychotics. SGAs are more useful when negative symptoms are prominent, clinical trials have shown that SGAs are effective in about 30% of non-responders to typical antipsychotics. Weight gain and impairment in glucose metabolism are common side effects of the SGAs. A study conducted in patients with chronic schizophrenia, showed that proportion of patients with bodyweight gain of >7% from baseline was 30%, 16%, 14%, 12% and 7% for olanzapine, quetiapine, risperidone, perphenazine and ziprasidone, respectively.[3] This excessive weight gain may lead to discontinuation of SGAs.

Various nonpharmacological and pharmacological strategies for prevention of weight gain and metabolic disturbance have been tried in patients treated with SGAs. Pharmacological intervention such as amantadine, famotidine, fluoxetine, fluvoxamine, metformin, nizatidine, orlistat, ranitidine, reboxetine, sibutramine, topiramate, have been found to decrease weight gain induced by SGAs.[4-6] Metformin is a antidiabetic agent belonging to biguanide , which also has role in individuals at

risk of developing insulin resistance due to conditions like polycystic ovary syndrome and premature puberty.[7,8] It is a hepatic-selective insulin sensitizer, it reduces weight, insulin resistance, and glycated haemoglobin (HbA_{1c}) in obese non diabetic adults.[9] It is also known to decrease insulin resistance and abnormal glucose metabolism resulting from the treatment with SGAs like olanzapine. But results obtained from previous studies regarding its benefit on reducing excessive weight gain induced by olanzapine is controversial and there is no data in Indian population, hence the present study was undertaken.

Aims

&

Objectives

AIMS AND OBJECTIVES

1. To study the effect of metformin on body weight, body mass index and waist to hip ratio in patients receiving olanzapine
2. To study the effect of metformin on blood glucose levels
3. To study the adverse effects of olanzapine and metformin using world health organization (WHO) causality assessment

Review Of Literature

REVIEW OF LITERATURE

Schizophrenia

"Like a stone thrown onto the smooth surface of a peaceful pond, schizophrenia disrupts lives in ever-expanding concentric circles, so that many lives and many people suffer the pain that arises from a single case."

Nancy Andreason, MD, Ph.D.

Historical Overview:

In prehistoric times, aberrant behaviour was ascribed to magic and religious notions of evil forces that invaded and inhabited a human body. The ignorance and fear associated with these behaviours resulted in victims being subjected to trephination and burning to free the evil forces. Hippocrates and Galen explained aberrant behaviour and madness by relating it to internal imbalances in the body. In the 18th century, Philippe Pinel, a French physician, believed that mental illness was a disease of the central nervous system and one that could be caused by hereditary or environmental factors. He instituted humane techniques to handle psychiatric patients and was also one of the early nosologists who categorized mental illness into subgroups and identified patients who had disturbances of intellect, emotion, or will.

Emil Kraepelin (1856–1926) a German psychiatrist was one of the first to distinguish manic-depressive psychoses from other chronic psychotic illnesses. Eugene Bleuler (1857–1939) was a Swiss psychiatrist who coined the term schizophrenia. In his paper entitled "Dementia praecox and the group of

schizophrenias," he put forth his theory that schizophrenia consisted of not just one illness with one etiological basis but a heterogeneous group of illnesses with distinguishing characteristics and clinical courses. He differed from Kraepelin in believing that these illnesses were not as often characterized by an early onset and a terminal dementia.

Bleuler's "four A's," as they are now commonly called, consisted of primary symptoms:

- Profound ambivalence
- A looseness of associations
- Disturbance of affect (either excitation or withdrawal)
- Autism, which he described as living in an internal, unrealistic world, separated from normal social interaction.

Kurt Schneider (1887–1967) from his own clinical experience, formulated a list of symptoms in his schizophrenia patients and described them as first and second rank, According to Schneider, the diagnosis of schizophrenia was appropriate if the patient experienced just one first-rank symptom; the second-rank symptoms, although common in schizophrenia, were not as specific.

Schneider's criteria for schizophrenia:

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 and several others as well

Epidemiology:

Schizophrenia is a severe form of mental illness affecting about 7 per thousand of the adult population, mostly in the age group 15-35 years. Though the incidence is low (3/10,000), the prevalence is high due to chronicity. It is prevalent in both urban and rural population, found in all societies and geographical areas, incidence and prevalence are roughly equal worldwide. [10] It is equally common in both genders but females have a relatively later age of onset of illness.[11, 12]

Etiopathogenesis

The neuropathology of schizophrenia is still unknown.

Heredity

Schizophrenia and related disorders are more in the first degree relatives of schizophrenics. However, the fact that the monozygotic twin of a schizophrenic patient has only a 50 percent chance of developing the disease implies that other factors must be involved.[13] Studies to locate schizophrenia gene and chromosomal segment which carries this gene have implicated several segments (3p, 6p, 6q, 8p, 13q, 22q), particularly the short arm of chromosome 6 (6p).[14]

Neuropathology

Injury during development: Some theories state that schizophrenia is a neurodevelopmental disorder resulting from neuronal injury in early years of fetal brain development. The injury results from prenatal and perinatal causes like infection and malnutrition of mother during pregnancy and prematurity, prolonged labour, hypoxia, and obstetric complications. This interferes with maturational events like glial proliferation and migration, axonal and dendritic proliferation, myelination of axons. Myelination continues even during adolescence in certain regions of the brain like prefrontal cortex which accounts for the long gap in the appearance of symptoms.[15]

Structural anomalies of brain: Brains of patients with schizophrenia are lighter and smaller. CT and MRI studies have brought to light several other findings. One of the most consistent finding is cerebral ventricular enlargement particularly the third and lateral ventricles. The enlargement is seen even in the first episode of illness, which

suggests that it is not due to neuroleptic medication. Frontal horn enlargement is seen in chronic cases whereas in non-chronic cases the temporal horns are enlarged. Sulci are widened and there is non-progressive cortical atrophy in about 50% of the patients. There is selective decrease in prefrontal cortex affecting its functions. In the limbic system, hippocampus, cingulated gyrus and amygdalae are involved and show reduced size and cytoarchitectural abnormalities. Studies have correlated reduction in size of the superior temporal gyrus with presence of auditory hallucinations.[16]

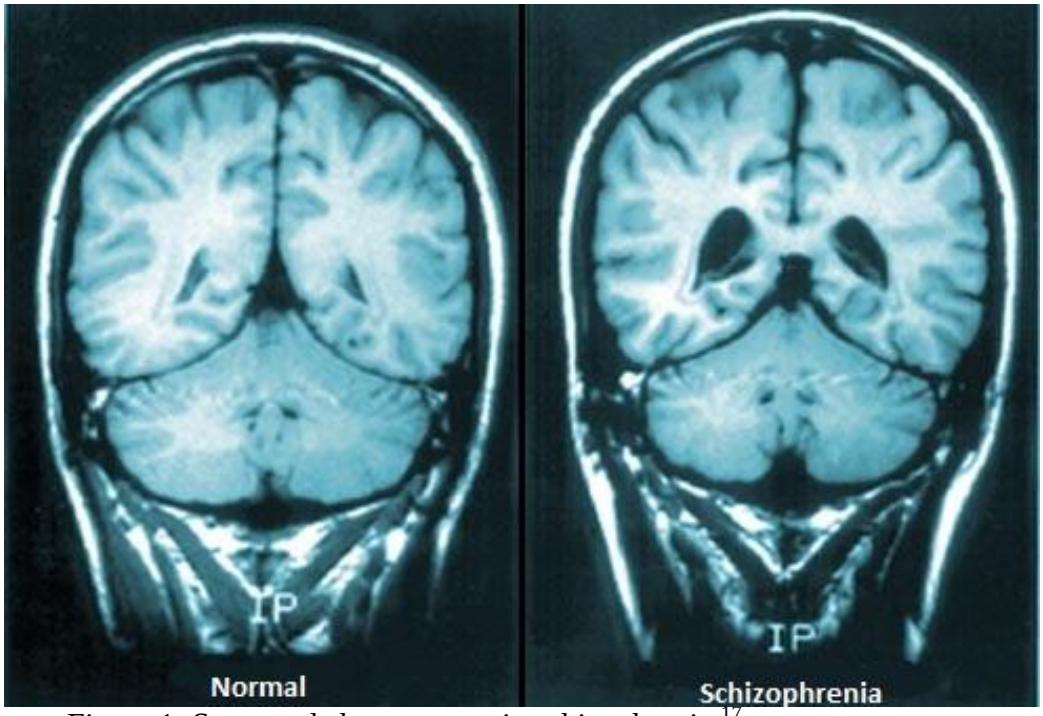

Figure 1: Structural changes seen in schizophrenia [17]

Physiological Changes: Functional circuitry refers to studies of regional blood flow using positron electron tomography (PET). A relative "hypofrontality" is seen associated with negative symptoms of schizophrenia. During execution of a "willed action" blood flow to the corresponding neural substrate is activated in normal people but this is reduced in schizophrenia. Blood flow is activated in sub-cortical regions and limbic areas during auditory hallucinations suggesting that hallucinations are generated or modulated in these areas and specified cortical areas.

Biochemical Factors

Dopamine hypothesis: The dopamine hypothesis suggests that schizophrenia is caused by functional hyperactivity of the dopamine system. The role of dopamine in the etiology of schizophrenia was suggested by two findings. Amphetamine and cocaine which release dopamine at central synapses induce schizophrenia-like symptoms in normals. In schizophrenics amphetamine worsens the symptoms. Secondly, the antipsychotic medicines given to control the schizophrenic symptoms, act by blocking the dopamine receptors and reducing dopamine over activity. Thus, it is believed that dopamine hyperactivity causes schizophrenic symptoms. Post-mortem studies also have shown that dopamine receptors of the D_2 type are dense in brain of schizophrenics.[18]

Glutamate and NMDA receptors: Glutamate is a major brain excitatory amino acid. Interest in glutamate and one of its several receptors, namely NMDA arose because phencyclidine induces schizophrenia-like psychosis. Phencyclidine is a non-competitive antagonist of the NMDA receptor, just like ketamine which also gives rise to schizophrenia-like symptoms. Also, glutamate levels are lowered in CSF and in post-mortem studies there is an increased NMDA receptor number. All these indicate that there is NMDA hypoactivity in schizophrenia.[19]

Serotonin hypothesis: Serotonin hypothesis predated dopamine hypothesis and held that both excess and deficiency caused schizophrenic symptoms. Interest in serotonin aroused in 1950s with the discovery of LSD psychosis which involved serotonin neurotransmission. Later with the discovery of atypical antipsychotics it was found that they have serotonin antagonistic properties which gave them the therapeutic

effect. An imbalance between serotonin and dopamine has been proposed as an etiological factor. [20]

GABA hypothesis: Gamma-amino butyric acid (GABA) activity is decreased in schizophrenics leading to increased dopamine activity. GABA is the main inhibitory neurotransmitter in the brain. Post-mortem studies show reduction in GABA in the neurons in the prefrontal cortex. Also, benzodiazepines which are agonists is of $GABA_A$ receptors relieve symptoms in some schizophrenic patients. [21]

Norepinephrine hypothesis: Increased norepinephrine activity is associated with increased dopamine activity and causes schizophrenic symptoms. [22]

Psycho-social Factors

Family as a cause of schizophrenia: Seroius pathology of the family environment was a consistent finding in many studies. Broken homes, unstable parents and eccentric child-rearing practices were seen in many cases. Two anomalous family situations leading to the onset of illness have been described. These are: (a) deviant rule relationship and (b) disordered communication. [23]

Clinical Features

The clinical features of schizophrenia are varied and can be grouped in several ways. One of the intended purposes of doing so in the past was to subgroup schizophrenia depending on the symptom complex. This was fruitless as many symptoms are not pathognomonic of schizophrenia, overlap each other and change over in the course of time. Another purpose was to simplify description of the elaborate symptoms. [24]

Positive and negative symptoms

In psychiatry, positive symptoms refer to those which are "actively expressed" such as hallucinations, delusions and bizarre motor acts, and are exaggeration or distortion of normal functions. Negative symptoms refer to deficit state of normal functions, like apathy and poverty of speech. These were correlated with other parameters like onset, course, therapeutic response, final outcome and biological correlates. It was hypothesized that positive and negative symptoms were the opposite poles of the same spectrum. Nearly one-third of all patients, however, share both groups of the symptoms. Factor analysis studies suggest that the positive symptoms themselves have two dimensions, one of psychotic symptoms and another of disorganization.[25]

The Five Dimensional Profile

Some studies subcategories symptoms of schizophrenia into five dimensions:

a. Positive symptoms
b. Negative symptoms
c. Cognitive symptoms
d. Aggressive/ Hostile symptoms
e. Effective symptoms[26]

Phenomenological Classification

Clinical features of schizophrenia can be descriptively classified as follows:

a. Disturbances of perception
b. Disturbances of thinking
c. Volitional disturbances

d. Disturbances of the mood

e. Other disturbances[27]

Classification

Schizophrenia can be classified into several subtypes. The catatonic and hebephrenic subtypes of schizophrenia together have been called as nuclear schizophrenia, as they present with typical symptomatology of schizophrenia and can most frequently result in personality deterioration over time.

According to ICD 10 schizophrenia has the following subcategories.

F20.0 Paranoid schizophrenia

F20.1 Hebephrenic schizophrenia

F20.2 Catatonic schizophrenia

F20.3 Undifferentiated schizophrenia

F20.4 Post schizophrenic depression

F20.5 Residual schizophrenia

F20.6 Simple schizophrenia

F20.8, F20.9 Others and unspecified

Diagnostic Criteria

The research diagnostic criteria (RDC) diagnosis of schizophrenia was divided into three groups; acute (lasting 2 weeks to 6 months); intermediate or sub-acute or sub-chronic (lasting 6 months to 2years); and chronic (illness present for at least 2years).

DSM-IV-TR Diagnostic Criteria for Schizophrenia [28]

A. *Characteristic symptoms*: Two (or more) of the following, 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 behaviour
   5. negative symptoms, i.e., affective flattening, alogia, or avolition

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.

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).

C. *Duration*: 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 Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. *Schizoaffective and mood disorder exclusion*: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. *Substance/general medical condition exclusion*: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. Relationship to a pervasive developmental disorder: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

ICD-10 (International Classification of Diseases) Diagnostic Criteria for Schizophrenia [29]

The schizophrenic disorders are characterized in general by fundamental and characteristic distortions of thinking and perception, and by inappropriate or blunted affect. Clear consciousness and intellectual capacity are usually maintained, although certain cognitive deficits may evolve in the course of time. The disturbance involves the most basic functions that give the normal person a feeling of individuality, uniqueness, and self-direction. The most intimate thoughts, feelings, and acts are often felt to be known to or shared by others, and explanatory delusions may develop, to the effect that natural or supernatural forces are at work to influence the afflicted individual's thoughts and actions in ways that are often bizarre. The individual may see himself or herself as the pivot of all that happens. Hallucinations, especially auditory, are common and may comment on the individual's behaviour or thoughts. Perception is frequently disturbed in other ways: colours or sounds may seem unduly vivid or altered in quality, and irrelevant features of ordinary things may appear more important than the whole object or situation. Perplexity is also common early on and frequently leads to a belief that everyday situations possess a special, usually sinister, meaning intended uniquely for the individual. In the characteristic schizo- phrenic disturbance of thinking, peripheral and irrelevant features of a total concept, which are inhibited in normal directed mental activity, are brought to the fore and utilized in place of those that are relevant and appropriate to the situation. Thus thinking becomes vague, elliptical, and obscure, and its expression in speech sometimes incomprehensible. Breaks and interpolations in the train of thought are frequent, and thoughts may seem to be withdrawn by some outside agency. Mood is characteristically shallow, capricious, or incongruous. Ambivalence and disturbance

of volition may appear as inertia, negativism, or stupor. Catatonia may be present. The onset may be acute, with seriously disturbed behaviour, or insidious, with a gradual development of odd ideas and conduct. The course of the disorder shows equally great variation and is by no means inevitably chronic or deteriorating (the course is specified by five-character categories). In a proportion of cases, which may vary in different cultures and populations, the outcome is complete, or nearly complete, recovery. The sexes are approximately equally affected but the onset tends to be later in women. Although no strictly pathognomonic symptoms can be identified, for practical purposes it is useful to divide the above symptoms into groups that have special importance for the diagnosis and often occur together, such as: (a)thought echo, thought insertion or withdrawal, and thought broadcasting; (b)delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception; (c)hallucinatory voices giving a running commentary on the patient's behaviour, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body; (d)persistent delusions of other kinds that are culturally inappropriate and completely impossible, such as religious or political identity, or superhuman powers and abilities (e.g. being able to control the weather, or being in communication with aliens from another world); (e)persistent hallucinations in any modality, when accompanied either by fleeting or half-formed delusions without clear affective content, or by persistent over-valued ideas, or when occurring every day for weeks or months on end; (f)breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms; (g)catatonic behaviour, such as excitement, posturing, or waxy flexibility, negativism, mutism, and stupor; (h)"negative" symptoms such as marked apathy, paucity of speech, and

blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance; it must be clear that these are not due to depression or to neuroleptic medication; (i)a significant and consistent change in the overall quality of some aspects of personal behaviour, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal.

Diagnostic guidelines

The normal requirement for a diagnosis of schizophrenia is that a minimum of one very clear symptom (and usually two or more if less clear-cut) belonging to any one of the groups listed as (a) to (d) above, or symptoms from at least two of the groups referred to as (e) to (h), should have been clearly present for most of the time during a period of 1 month or more. Conditions meeting such symptomatic requirements but of duration less than 1 month (whether treated or not) should be diagnosed in the first instance as acute schizophrenia-like psychotic disorder (F23.2) and reclassified as schizophrenia if the symptoms persist for longer periods. Symptom (i) in the above list applies only to the diagnosis of Simple Schizophrenia (F20.6), and duration of at least one year is required. Viewed retrospectively, it may be clear that a prodromal phase in which symptoms and behaviour, such as loss of interest in work, social activities, and personal appearance and hygiene, together with generalized anxiety and mild degrees of depression and preoccupation, preceded the onset of psychotic symptoms by weeks or even months. Because of the difficulty in timing onset, the 1-month duration criterion applies only to the specific symptoms listed above and not to any prodromal nonpsychotic phase. The diagnosis of schizophrenia should not be made in the presence of extensive depressive or manic symptoms unless it is clear that schizophrenic symptoms antedated the affective disturbance. If both schizophrenic and affective symptoms develop together and are evenly balanced, the

diagnosis of schizoaffective disorder (F25.-) should be made, even if the schizophrenic symptoms by themselves would have justified the diagnosis of schizophrenia. Schizophrenia should not be diagnosed in the presence of overt brain disease or during states of drug intoxication or withdrawal. Similar disorders developing in the presence of epilepsy or other brain disease should be coded under F06.2 and those induced by drugs under F1x.5.

Pattern of course

The course of schizophrenic disorders can be classified by using the following five-character codes:

F20.x0 Continuous

F20.x1 Episodic with progressive deficit

F20.x2 Episodic with stable deficit

F20.x3 Episodic remittent

F20.x4 Incomplete remission

F20.x5 Complete remission

F20.x8 Other

F20.x9 Course uncertain, period of observation too short

Course and Prognosis

The course of schizophrenia is generally a chronic one though it differs considerably showing individual variations. Long before a full-fledged clinical picture sets in, "character anomalies" may appear as subtle indications of an oncoming illness in later life. These are in the form of delay in development of specific skills and other deficits symptoms as well as tendency for social aloofness and maladjustment. Often a prodromal stage with an insidious onset and where the above features become more prominent precede the active phase of illness. The clinical features become florid in the active phase and the patient is brought to the hospital invariably at this stage. After the violation of the active phase with proper treatment, a residual phase may follow which resembles the prodromal phase of the illness.[30]

The residual symptoms may persist and may not totally disappear in a good proportion of patients. But many long-term studies have shown that the course of illness is not uniform and the outcome is not bleak as was once believed. A few recover totally and are asymptomatic for several years. Some continue to relapse with stable or worsening deficits. A good number of patients are able to meet their basic needs and many among them show good social functioning.[31]

Prognosis is worse in hebephrenia and simple schizophrenia. Some points to a good prognosis are:

1. Absence of family history of schizophrenia
2. Stable premorbid personality
3. Acute onset with short duration
4. Presence of precipitating factors
5. Preservation of affect

6. Good support systems

   As per the International Pilot study of Schizophrenia conducted by WHO in 1975 five powerful indicators of a poor outcome are:

   a) History of behavioral problems in childhood
   b) Social isolation
   c) Unmarried status
   d) History of previous psychiatric illness
   e) Long duration of illness

      The study showed that outcome was generally better for patients in developing countries than in industrialized ones, possibly due to better social anchoring in the former group. Female patients fare better than their male counterparts.[32]

Management of schizophrenia:

Treatment of schizophrenia fall under two categories:

1. Somatic treatment :
   a) Pharmacological treatment
   b) Electro-convulsive therapy (ECT)
   c) Miscellaneous treatments
2. Psychosocial treatment and rehabilitation

Pharmacological treatment

The first drug to be used with beneficial effect in schizophrenia was reserpine in India by Sen and Bose (1931), which is no longer used due to its propensity to cause severe depression. SGAs such as risperidone, olanzapine, quetiapine, aripiprazole and ziprasidone are more commonly used than the older typical or first generation antipsychotics such as trifluoperazine and haloperidol, in acute stages. SGAs are also more useful when negative symptoms are more prominent. Clozapine, another SGA, is shown to be effective in about 30% of patients who had no beneficial response to traditional antipsychotics. It is an effective drug but should be used with caution as it can cause agranulocytosis and seizures as side effects.

In the presence of acute excitement, haloperidol 5mg IV or IM, with/without 10mg diazepam or 50mg of promethazine can be administered. A majority of patients require maintenance treatment with antipsychotics to prevent relapse. Generally, the treatment is continued for six months to one year for the first episode, for 1-2 years for the subsequent episodes and for indefinite period for repeated episodes or persistent symptoms. However, the decision regarding the duration of treatment in a particular patient has to be assessed by the treating psychiatrist in consultation with the patient and the family. To ensure drug complaince, depot antipsychotic preparations with long duration of action can be used.

Antipsychotics probably act by blocking the post synaptic dopamine (D_2) receptors in the mesolimbic system. Other receptors such as 5-HT, muscarinic receptors and GABA are also probably important. SGAs are also called as serotonin-dopamine antagonists due to their action on both dopamine and 5-HT.[33]

Table No 1: Antipsychotics[33]

Drug Class	***Drug***	Dose (mg/day)
Butyrophenones	Haloperidol	5-30
Phenothiazines	Thioridazine	300-600
Aliphatic	Chlorpromazine	400-1000
Piperazine	Trifluoperazine Prochlorperazine	15-50 45-150
Thioxanthines	Flupentixol Zuclopenthixol	3-18 25-150
Diphenylbutylpiperidines	Pimozide	4-12
Benzmides	Sulpiride Amisulpride	400-2400 400-1200
Dibenoxazepine tricyclics	Loxapine Clozapine	25-250 50-900
Thienobenzodiazepines	Olanzapine Quetiapine Zotepine	5-20 150-800 75-300
Serotonin-dopamine Antagonists	Risperidone Ziprasidone	2-16 40-160

Electro-convulsive therapy

Schizophrenia is not a primary indication for ECT. The indications for ECT in schizophrenia include:

1. Catatonic stupor
2. Uncontrolled catatonic excitement
3. Acute exacerbation not controlled with drugs
4. Severe side effects with drugs, in presence of untreated schizophrenia

Usually 8-12 ECTs are needed, administered two to three times per week.

Miscellaneous treatment

Psychosurgery is not routinely indicated in the treatment of schizophrenia. It is rarely used in clinical practice. When used, the treatment of choice is limbic leucotomy (a small subcaudate lesion with cingulated lesion) in some cases with severe and very prominent depression, anxiety or obsessional symptoms. Severely deteriorated patients are unlikely to benefit. The maximum benefit would be in acute episodes, but antipsychotics are far better in efficacy and safety.

Many other methods such as megavitamin therapy, dialysis, malaria therapy, high dose propranolol and insulin coma therapy have been used in past but are no longer used in clinical practice due to either poor evidence for efficacy and risks to the patient.

Psychosocial treatment and rehabilitation

Psychological methods of treatment like individual psychotherapy, family therapy and group therapy are useful along with antipsychotic medications with good results. They help to improve compliance to treatment and ensure better social and

occupational functioning and early rehabilitation. They also prevent relapses. The specific method depends on the nature of illness, condition of the patient, phase of the illness and social support available. Family therapy and group therapy which promote social skills are used with advantage in schizophrenics. Family therapy can reduce the relapse rate for the schizophrenic family member. Psychological rehabilitation aims at integrating patients back to the community instead of segregating them. This takes into consideration the skills and talent of the patient and involves medication, psycho-social interventions and foster institutions.[34]

PHARMACOLOGY OF OLANZAPINE

Olanzapine is an atypical antipsychotic, approved by the U.S. Food and Drug Administration (FDA) on 30th September 1996, for the treatment of schizophrenia and bipolar disorder. Olanzapine, a thienobenzodiazepine derivative, belongs to class of second generation antipsychotic agents.

Olanzapine Chemistry:

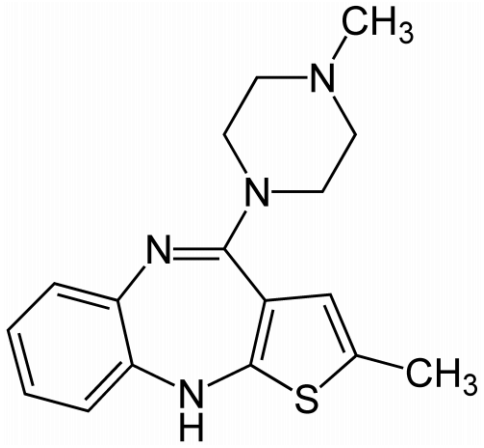

Figure 2: The chemical structure of olanzapine[35]

Chemical name/IUPAC name :

2-Methyl-4-(4-methyl-1-piperazinyl)-10-thieno[2,3-*b*] [1,5] benzodiazepine

Molecular formula: $C_{17}H_{20}N_4S$

Molecular weight: 312.439

Physical property: Yellow crystalline solid and insoluble in water.

Pharmacodynamics:

The binding profile indicates that olanzapine has high affinity for 5-HT_{2A}, $5HT_{2B}$, 5-HT_{2C} and 5-HT_6 and histamine (H_1) receptors, as well as a moderate affinity for D_2 and acetylcholine muscarinic receptors, and a low affinity for β-adrenergic receptors. Olanzapine also interacts non-selectively with other dopamine receptors and 5-HT_1, 5-HT_3, 5-HT_4 and 5-HT_7 receptors.[36]

Mechanism of action:

The mechanism of action is not completely understood. Antipsychotic effects may be related to blockade of dopamine (D_1, D_2, D_3, D_4), serotonin ($5HT_2$, $5HT_3$, $5HT_6$), histamine (H_1), alpha-1 adrenergic and muscarinic (M_1-M_5, particularly M_1) receptors. Typical antipsychotics such as the phenothiazines (e.g. chlorpromazine) or the butyrophenones (e.g. haloperidol) strongly block dopamine receptors. In contrast, olanzapine blocks serotonin receptors ($5HT_2$) more strongly than dopamine (D_2) receptors. Blockade of $5HT_2$ receptors is a proposed mechanism for effects on negative symptoms in schizophrenia. Muscarinic blocking (anticholinergic) effects and lower affinity for dopamine receptors may possibly account for the decreased incidence of extrapyramidal symptoms (EPS) seen with olanzapine. Effect on prolactin levels is minimal.[37]

Pharmacokinetics

Olanzapine is well absorbed after oral administration reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food. The plasma protein binding of olanzapine is about 93%, it is bound predominantly to albumin and α1- acid glycoprotein. Volume of distribution of olanzapine is 10-18L/kg. In both,

young and elderly, steady-state concentrations of olanzapine is obtained after seven days of once daily dosing. Concentration of 23ng/ml is required to produce anti-schizophrenic effect.[38]

Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which is pharmacologically inactive and does not pass the blood brain barrier. Cytochrome P450 isoforms CYP1A2 and CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites. Both metabolites exhibit significantly less pharmacological activity than olanzapine. About 57% of a dose is excreted in the urine, mainly as metabolites and about 30% appears in the feces. The mean plasma elimination half-life has been variously reported to be about 30 and 38 hours.[39]

INDICATIONS AND CLINICAL USE

Schizophrenia and Schizoaffective Disorders:

Olanzapine is indicated for the acute and maintenance treatment of schizophrenia and schizoaffective disorders. It improves both positive and negative symptoms.[40-43]

Bipolar Disorder:

Olanzapine is indicated for the acute treatment of manic or mixed episodes in bipolar disorder. Olanzapine may be used as monotherapy or co-therapy with agents commonly used in the treatment of acute bipolar disorder (e.g., lithium or divalproex sodium).[44-46]

Adverse Effects of Olanzapine:

The most frequent adverse effects of olanzapine are somnolence and weight gain, hyperprolactinemia. Increased appetite, dizziness, fatigue, elevated plasma glucose, triglycerides and liver enzyme values, edema, orthostatic hypotension and mild transient constipation and dry mouth are also relatively common.[47-50] Blood dyscrasias including agranulocytosis, eosinophilia, leucopenia, neutropenia and thrombocytopenia have also been reported.[51-53] Weight gain, sedation and liver enzyme values, lipid and prolactin alterations may be greater in adolescence than in adults. Severe hyperglycemia or exacerbation of preexisting diabetes, sometimes lead to ketoacidosis, coma, or death. Clinical monitoring for hyperglycemia has been recommended, especially in patients with or at risk of developing diabetes. Monitoring of weight and plasma lipids have also been recommended.[54-57]

Olanzapine is associated with a low incidence of extrapyramidal effects, including tardive dyskinesia, although these effects may be more likely at high doses and in the elderly; the risk of tardive dyskinesia also increases with long term use. Neuroleptic malignant syndrome has been reported rarely.

Patients receiving olanzapine intramuscularly should be closely observed for 2-4 hours for hypotension, bradyarrythmias and hypoventilation. Intramuscularly route should be avoided in patients with a history of cardiovascular disease or after heart surgery; caution is recommended when giving olanzapine orally to such patients and to those with cerebrovascular disease or conditions predisposing to hypotension. It is recommended that blood pressure is periodically assessed in elderly patients.[58]

When olanzapine is used for the depressive phase in bipolar disorder or for unipolar depression, patient should be closely monitored during early therapy until

significant improvement in depression occurs because suicide is an inherent risk in depressed patients. Withdrawal symptoms including sweating, tremor, anxiety, nausea and vomiting have occurred rarely when olanzapine have been stopped abruptly; gradual dose reduction may be appropriate when stopping olanzapine.

CONTRAINDICATIONS AND PRECAUTIONS:

The anti-muscarinic effects of olanzapine contraindicate its use in patients with angle closure glaucoma; caution is also advised in those with conditions such as benign prostatic hyperplasia or paralytic ileus. Olanzapine is also not recommended in parkinsons disease since its use has commonly been associated with an increase in parkinsonian symptoms and hallucinations. It should be used with caution in patients with hepatic impairment, or history of blood dyscrasias, bone marrow depression, or myeloproliferative disease. Seizures are rare with olanzapine but it should be used with care in those with history of seizure or with conditions that lower the seizure threshold.[59]

DRUG INTERACTIONS:

The central effects of other CNS depressants, including alcohol, may be enhanced by olanzapine. Olanzapine may antagonize the effects of dopaminergics. Neutropenia may be more common when olanzapine is given with valproate.[60] Use with valproate or lithium has also been associated with an increased incidence of tremor, dry mouth, increased appetite and weight gain. There may be a risk of QT prolongation when olanzapine is given with other drugs that are known to cause this effect.

Drugs that induce hypotension, bradycardia or respiratory depression should be used with caution in patients given intramuscular olanzapine. Parenteral benzodiazepine treatment should be given at least one hour after intramuscular olanzapine as it is recommended that they are not given together.

The metabolism of olanzapine is mediated by the cytochrome P450 isoenzyme CYP1A2. Use with drugs that inhibit, induce or act as substrate to this isoenzyme may affect plasma concentration of olanzapine and a dose adjustment of olanzapine may be required. The CYP1A2 inhibitor fluvoxamine significantly inhibits the metabolism of olanzapine. The clearance of olanzapine is increased by tobacco smoking and carbamazepine.[61]

PHARMACOLOGY OF METFORMIN

HISTORY:

Metformin was first described in the scientific literature in 1922 by Emil Werner and James bell, as a product in the synthesis of N,N-dimethylguanidine. In 1929, Slotta and Tschesche discovered its sugar lowering action in rabbits, noting it was the most potent of the biguanide analogues they studied. This result was completely forgotten, as other guanidine analogues such as the synthalins, took over, and were themselves soon over shadowed by insulin. Interest in metformin, however, picked up at the end of the 1940s. In 1950, metformin, unlike some other similar compounds, was found not to decrease blood pressure and heart rate in animals.[62]

French diabetologist Jean Sterne was the first to try metformin on humans for the treatment of diabetes; he coined the name "Glucophage" for the drug and published his results in 1957. Metformin became available in the British National Formulary in 1958. Metformin was approved in Canada in 1972, US FDA approved it for treatment of type 2 diabetes in 1995.[63]

METFORMIN CHEMISTRY:

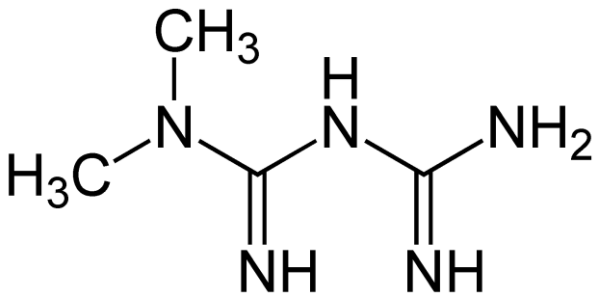

Figure 3: The chemical structure of Metformin[64]

Chemical name/IUPAC name: N,N-Dimethylimidodicarbonimidic diamide

Molecular formula: $C_4H_{11}N_5$

Molecular weight: 129.163

Physical property: White powder, odorless and hygroscopic, easily soluble in water.

Mechanism of Action

Metformin increases the activity of the AMP-dependent protein kinase (AMPK). AMPK is activated by phosphorylation when cellular energy stores are reduced. Activated AMPK stimulates fatty acid oxidation, glucose uptake and nonoxidative metabolism and it reduces lipogenesis and gluconeogenesis.[65] The net result of these actions is increased glycogen storage in skeletal muscle, lower rates of hepatic glucose production, increased insulin sensitivity and lower blood glucose levels.[66, 67]

Molecular mechanism by which metformin activates AMPK is not known, it is thought to be indirect, possibly by reducing intracellular energy stores. Consistent with this, metformin has been shown to inhibit cellular respiration by specific actions on mitochondrial complex I. Metformin has little effect on blood glucose in normoglycemic states and does not affect the release of insulin or other islet hormones and rarely causes hypoglycemia. However, even in persons with only mild hyperglycemia, metformin lowers blood glucose by reducing hepatic glucose production and increasing peripheral glucose uptake. This effect is partially mediated by reducing insulin resistance at key target tissues. The hepatic effect is probably the dominant mode of action and involves primarily suppression of gluconeogenesis.[68, 69]

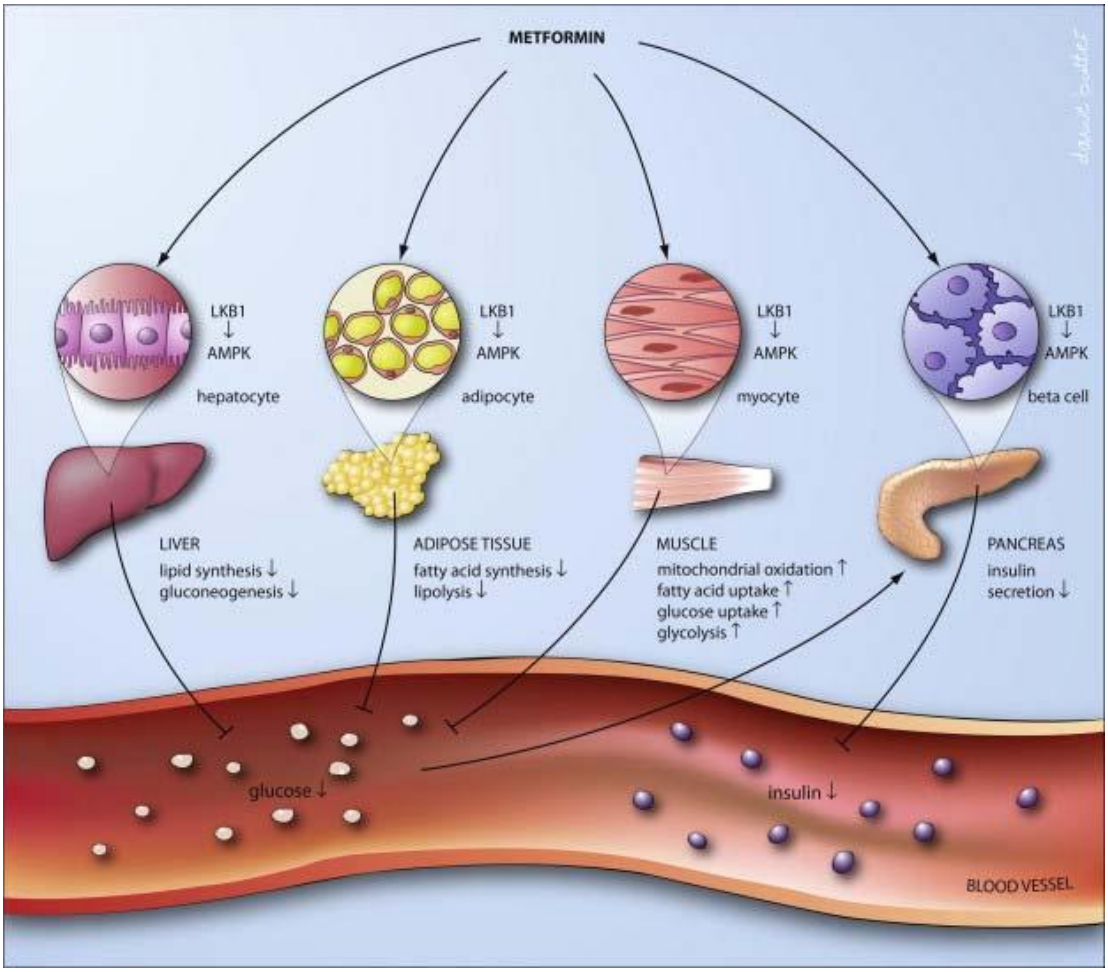

Figure 4: Metformin mechanism of action[70]

The mechanisms of metformin effects in PCOS pertain to its central and peripheral action. At the central level, the possible effect is reduction in serum LH level. At the peripheral level, metformin decreases hepatic gluconeogenesis, increases the synthesis of sex hormone-binding globulin (SHBG), consecutively decreasing free androgen levels. Metformin also increases insulin sensitivity in peripheral tissues, reduces free fatty acid oxidation, and reduces ovarian and adrenal secretion of androgens. Pleiotropic actions of metformin are mediated by the AMPK pathway. [71, 72]

PHARMACOKINETICS:

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. The apparent volume of distribution of metformin is 654±358L. Metformin is negligibly bound to plasma proteins. Metformin crosses placenta and is distributed to breast milk in small amounts.[73, 74]

Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism, renal clearance is approximately 3.5 times greater than creatinine clearance which indicates that tubular secretion is the major route of metformin elimination. Plasma elimination half-life is approximately 2 to 6 hours.[75]

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen of metformin for the management of hyperglycemia in patients with type 2 diabetes. Dosage of metformin must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose. The maximum recommended daily dose of metformin hydrochloride tablets is 2550 mg in adults.[76] Metformin should be given in divided doses with meals and should be started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.[77]

INDICATIONS

Metformin is indicated in the treatment of type 2 diabetes mellitus in adults, children from 10 years of age and adolescents, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycemic control. For adult patients, metformin may be used as initial treatment or in sulfonylurea failures either alone or in combination with a sulfonylurea and other oral agents or as adjuvant therapy in insulin requiring type 2 diabetes.[78, 79]

ADVERSE EFFECTS

Mild gastrointestinal symptoms such as anorexia, nausea, vomiting, diarrhea and abdominal pain are the most frequent reactions to metformin, especially during the initial treatment period. These symptoms are generally transient and resolve spontaneously during continued treatment. Gastrointestinal side effects can possibly be avoided if metformin is taken with meals and if the dose is increased slowly.[80]

Lactic acidosis is a very rare but serious metabolic complication that can occur due to metformin accumulation during treatment with metformin.[81] Patient may have taste disturbance (metallic taste) and weight loss. Absorption of vitamin B_{12} may be impaired during long-term use of metformin.[82]

CONTRAINDICATIONS

- Unstable and/or insulin-dependent (Type I) diabetes mellitus
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis
- In patients with a history of lactic acidosis, irrespective of precipitating factors

- In the presence of renal impairment or when renal function is not known, and also in patients with serum creatinine levels above the upper limit of normal range
- In excessive alcohol intake, acute or chronic
- In patients suffering from severe hepatic dysfunction, since severe hepatic dysfunction has been associated with some cases of lactic acidosis, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease
- In cases of cardiovascular collapse and in disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia
- During stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter
- In patients suffering from severe dehydration
- Known hypersensitivity or allergy to metformin or any of the excipients
- During pregnancy and breastfeeding[83]

DRUG INTERACTIONS

Certain drugs may potentiate the effect of metformin, particularly sulfonylurea type of drugs in the treatment of diabetes. The simultaneous administration of these two types of drugs could produce hypoglycemia. In general fewer drug interactions have been reported with metformin. Alcohol may increase the risk of lactic acidosis as well as hypoglycemia. Care should be taken if metformin is given with drugs that may impair renal function.[84]

Materials & Methods

MATERIALS AND METHODS

This study was conducted from Jan 2013 to June 2014, in patients clinically diagnosed with schizophrenia and bipolar disorder as per ICD10.[29]

Location of study:

This study was conducted on outpatients, attending the Department of Psychiatry at R.L.Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Data collection:

A proforma containing detailed information of each patient was designed according to the study protocol. Ethical clearance was obtained from Institutional Ethics Committee. Written informed consent was obtained from patients and/or their care takers.

Inclusion Criteria

1. Patients between 18-50 years of either gender
2. Schizophrenia and bipolar mania patients diagnosed in accordance with criteria established in ICD10

Exclusion Criteria

1. Patients with addictive disorders (smoking, alcoholism)
2. Patients with specific systemic disease (Diabetes Mellitus, Hypertension, Epilepsy, Coronary Artery Disease)
3. Pregnant and lactating women

Method of collection of data:

Patients diagnosed with schizophrenia and bipolar disorder, planned for treatment with olanzapine on outpatient basis were recruited and randomized into two groups. Group A received olanzapine 10mg/day at 8pm and metformin 850mg/day in the morning for 12 weeks and Group B received olanzapine alone for 12 weeks. Baseline assessments included demographic details, medical history, diet history and physical examination such as anthropometric measurements like Weight, Height and Body Mass Index (BMI), Waist circumference, Hip circumference and Waist to hip ratio. Fasting blood glucose (FBS) level was measured at baseline. Follow-up visits were done at 4, 8 and 12 weeks. At each follow-up visit physical examination and anthropometric measurements were repeated. FBS was re-evaluated at week 12. Weight was measured using a digital scale; waist and hip circumference were measured using a measuring tape. Waist circumference was measured at the level which is midway between lowest point of ribs and anterior superior iliac spine and hip circumference at the level of the greater trochanters.

Statistical Methods

With power of 80%, α error 5% and to detect a difference of 3.88kg weight loss, the required sample size with 10% dropout was 31 patients per group. Demographic data were expressed as mean and standard deviation. Weight, BMI, waist circumference, hip circumference, waist to hip ratio and FBS were analyzed using paired and unpaired t-test. Repeated measures ANOVA was used to analyze weight, BMI, waist circumference, hip circumference, waist to hip ratio parameters within the group at different time intervals. Chi square test was used to analyze patients achieving >7% weight gain and adverse effects. p value of <0.05 was considered significant.

Results

RESULTS

A total of 65 patients who satisfied the inclusion criteria and clinically diagnosed with schizophrenia and bipolar mania as per ICD 10 were randomized into two groups. Patients in group A received olanzapine 10mg plus metformin 850mg and group B olanzapine 10mg once daily. Fifty nine patients completed the 12 weeks treatment, two patients were lost to follow up at 4th week and one patient was excluded from the study due to adverse effects in group A. One patient was lost to follow up at 8th week and two were excluded due to change in treatment to avoid further weight gain of more than 10% in group B.

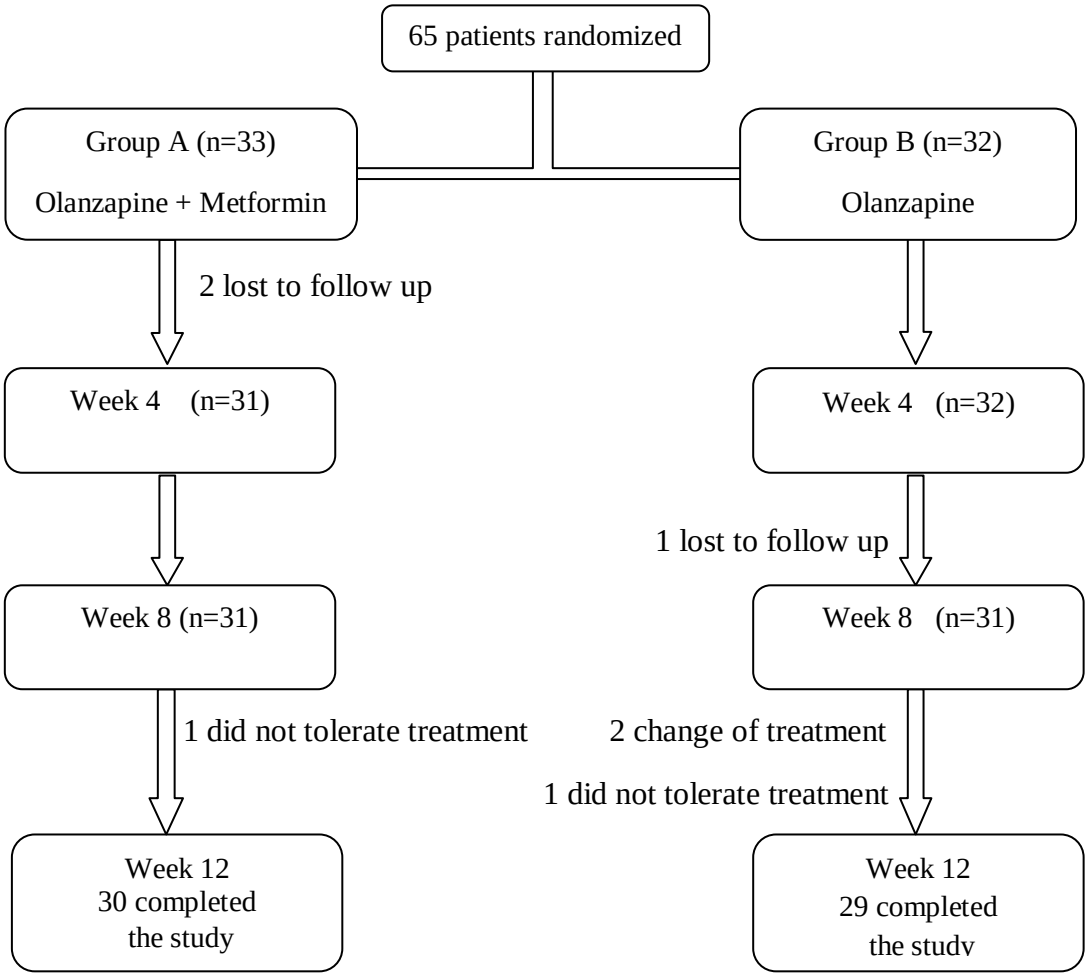

Figure 5: Flow chart representing randomization and follow up of patients

Table 2: Demographic data and duration of disease

Parameters	Group A n=33	Group B n=32	p value
Age(years)±SD	36.06±10.01	33.06±7.14	0.72
Gender Male (%) Female (%)	 15 (45.5) 18 (54.5)	 14 (43.8) 18 (56.2)	0.89
Duration of disease(months)±SD	8.86±7.21	9.96±7.96	0.57

There were 29 males and 36 females in our study. Demographic data and the duration of disease were similar in both groups.

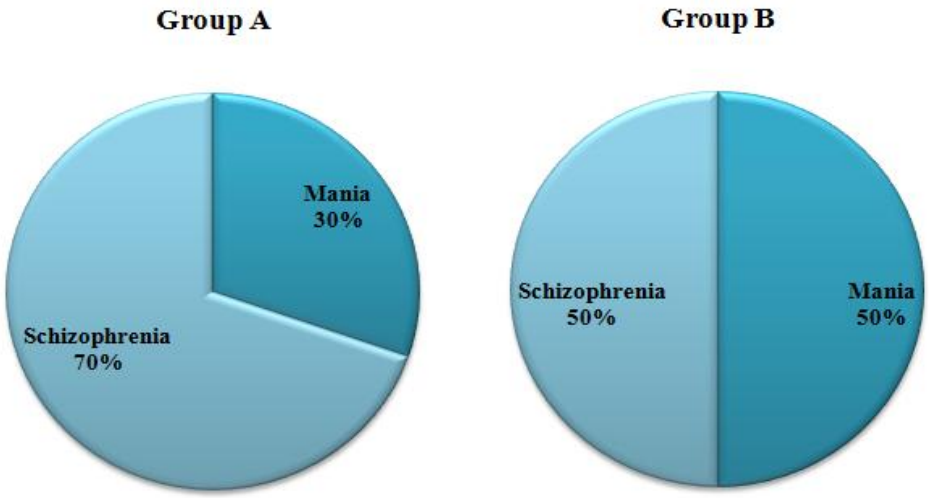

Figure 6: Types of psychiatric illness expressed as percentage

Table 3: Baseline anthropometric measurements and fasting blood sugar

Parameters	Group A (Mean±SD) n=33	Group B (Mean±SD) n=32	p value
Weight (kg)	51.03±11.47	49.83±10.60	0.66
BMI (kg/m^2)	20.40±3.46	20.24±3.42	0.84
Waist circumference (cm)	74.24±11.09	72.62±10.66	0.55
Hip Circumference (cm)	88.70±9.74	88.19±8.67	0.82
Waist to Hip ratio	0.833±0.07	0.821±0.06	0.49
FBS (mg/dl)	90.15±10.64	94.34±8.46	0.08

All the baseline parameters were comparable between the groups at the time of recruitment.

Table 4: Comparison of weight and BMI at different time intervals

Variable	Group A (Mean±SD) n=30	Group B (Mean±SD) n=29	p value
Weight			
Baseline	50.37±10.11	49.20±10.16	0.65
4 weeks	51.96±9.53*	51.94±9.88*	0.99
8weeks	52.85±9.67*	53.84±9.88*	0.69
12weeks	53.66±9.74*	55.22±9.41*	0.53
BMI			
Baseline	20.49±3.35	20.15±3.29	0.69
4 weeks	21.16±3.15*	21.32±3.06*	0.84
8weeks	21.54±3.27*	22.11±3.04*	0.48
12weeks	21.88±3.38*	22.69±2.92*	0.32

*p = 0.001 compared with baseline within the group

Change in body weight, BMI, waist circumference, hip circumference and waist to hip ratio were assessed only in patients who completed the 12 week study. Body weight and BMI increased in both the groups, which were significant at week 4, 8 and 12 when compared with baseline (p = 0.001). The change in weight and BMI between groups was not statistically significant.

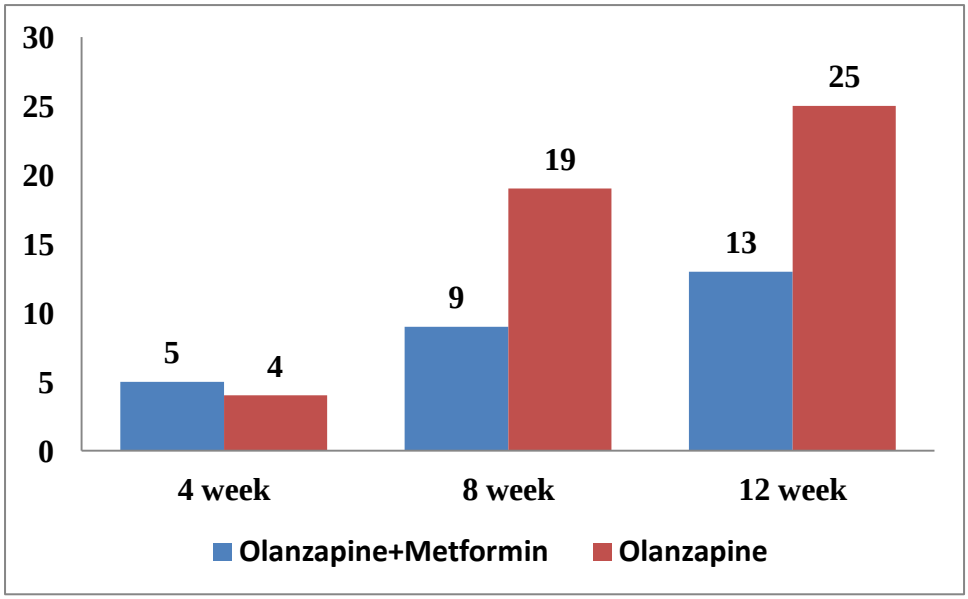

Figure 7: Number of patiens who gained more than 7% body weight

Patients who gained weight of more than 7% at different intervals of time in both the groups were compared. At week 4 there was no statistically significant difference, but at weeks 8 and 12 it was significant with p=0.006 and 0.001 respectively.

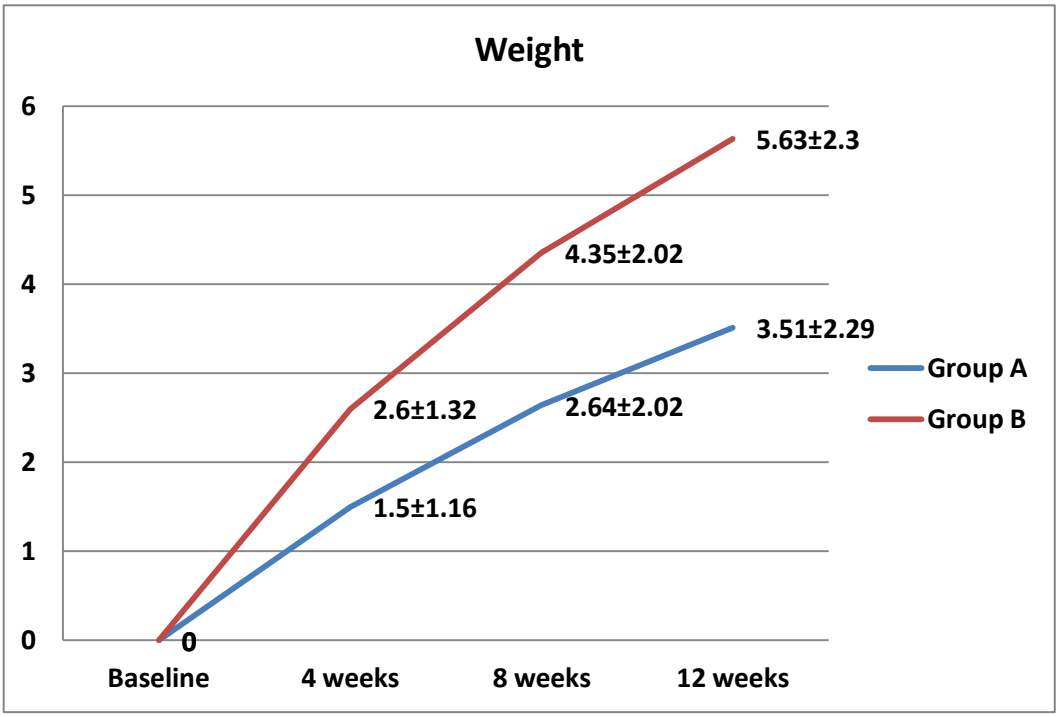

Figure 8: Changes in body weight

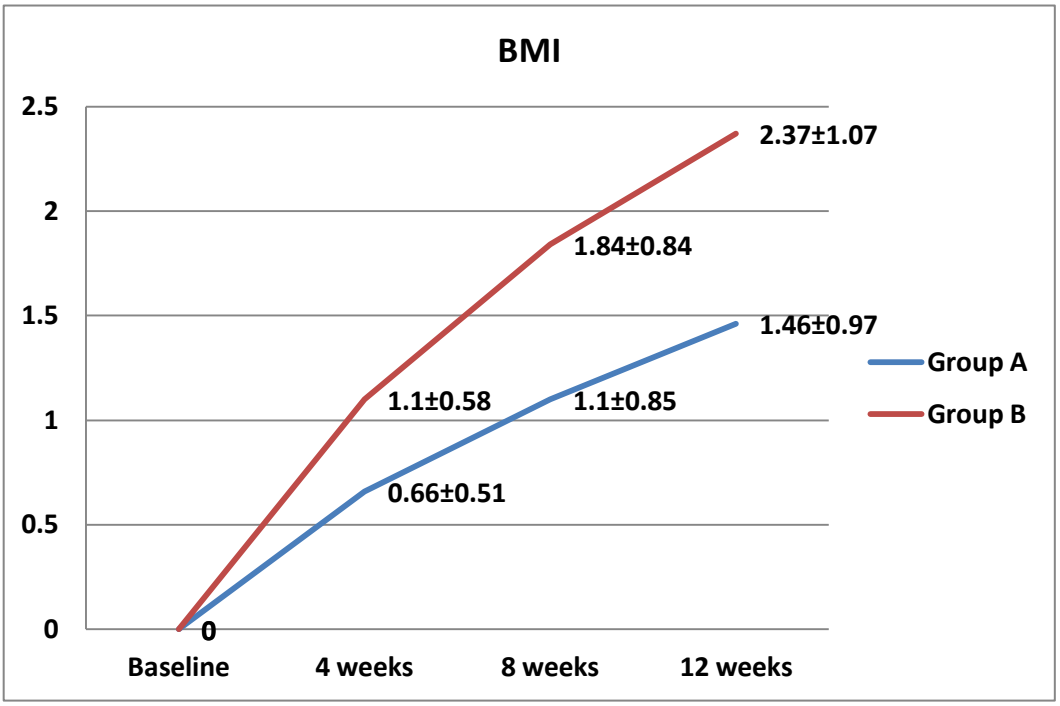

Figure 9: Changes in body mass index

The actual difference in weight and BMI of individual patients from baseline to week 4, 8 and 12 was assessed. Percentage change in terms of weight gain from baseline to end of the study was 6.43% and 10.16% in metformin plus olanzapine and olanzapine alone respectively which was statistically significant. Between group analysis of the above parameters at various intervals showed that olanzapine induced weight gain and BMI was prevented by metformin which was significant (p = 0.001). This finding was observed when other confounding factors like age, diet, physical activity were not controlled, as it was very difficult in these patients to counsel them for these factors.

Table 5: Comparison of waist circumference, hip circumference and waist to hip ratio

Variable and Week	**Group A (Mean±SD) n=30**	**Group B (Mean±SD) n=29**	**p value**
Waist circumference (cm)			
Baseline	74.43±10.48	72.37±10.37	0.45
4 weeks	75.63±10.13*	74.37±9.89*	0.63
8weeks	76.26±10.37*	75.79±10.04*	0.85
12weeks	76.76±10.38*	76.86±9.83*	0.97
Hip circumference (cm)			
Baseline	89.00±9.72	87.82±8.48	0.62
4 weeks	89.83±9.61*	89.10±8.43*	0.75
8weeks	90.53±9.71*	89.96±8.57*	0.81
12weeks	91.03±9.77*	91.06±8.60*	0.98
Waist to Hip ratio			
Baseline	0.833±0.070	0.822±0.069	0.54
4 weeks	0.835±0.064*	0.833±0.064*	0.91
8weeks	0.841±0.068*	0.841±0.065*	0.97
12weeks	0.842±0.068*	0.846±0.064*	0.86

*p = 0.001 compared with baseline within the group

Waist circumference and hip circumference increased significantly in both the group when compared to baseline, but no difference was observed in patients receiving olanzapine plus metformin and olanzapine alone. Similar findings were observed for waist to hip ratio, except for its correlation which showed no association with weight change, where as a weak positive correlation was seen with waist circumference and hip circumference.

Table 6: Fasting blood sugar

Fasting Blood Sugar	Group A	Group B	p value
Baseline	94.61±10.68	94.34±8.46	0.80
12 weeks	90.15±10.64*	95.66±9.00	0.049

p = 0.03 when compared with baseline

FBS values were within the normal range in both the groups and were comparable at baseline. In patients receiving olanzapine plus metformin there was decrease in fasting FBS level at week 12 compared to baseline which was significant but not in patients receiving only olanzapine. When FBS was compared between the groups at the end of the study there was significant decrease, in patients receiving metformin and olanzapine than those who received only olanzapine.

One patient who received metformin plus olanzapine had abdominal pain and constipation and one patient who received only olanzapine had severe weakness and somnolence. According to WHO causality scale both the reactions were graded as probable and both these patients were withdrawn from the study and were not included in the analysis.

Discussion

DISCUSSION

Schizophrenia is a chronic, severe and disabling brain disorder that has affected people throughout history. Positive symptoms of schizophrenia include delusion, hallucinations, thought disorders, catatonia, abnormal and disorganized behaviour. Negative symptoms are withdrawal from social contacts, flattening of emotional responses, anhedonia, reluctance to perform everyday tasks. A combination of factors can predict schizophrenia in up to 80 percent of youth who are at high risk of developing the illness. These factors include isolating oneself and withdrawing from others, an increase in unusual thoughts and suspicions, and a family history of psychosis. In young people who develop the disease, this stage of the disorder is called the "prodromal" period.

The neuropathology of schizophrenia is still not fully understood but is believed to be caused by several factors which includes genes and environmental, neurodevelopmental disorder resulting from neuronal injury in early years of fetal brain development, structural anomalies of brain like cerebral ventricular enlargement particularly the third and lateral ventricles. The biochemical factors include hyperactivity of the dopaminergic system, NMDA hypoactivity, imbalance between serotonin and dopamine, decreased gamma-amino butaric acid (GABA) and increased norepinephrine activity.

Schizophrenia is managed using antipsychotics and various psychosocial treatments. Antipsychotics act by blocking the post synaptic dopamine (D_2) receptors in the mesolimbic system and other receptors such as 5-HT, muscarinic receptors and GABA. Second generation antipsychotics (SGAs) act as antagonists at dopamine and 5-HT receptors. SGAs such as aripiprazole, clozapine, olanzapine, resperidone,

quetiapine, ziprasidone, amisulpride, zotepine and sertindole are more commonly used than typical antipsychotics. They are more effective when negative symptoms are prominent but weight gain and impairment in glucose metabolism are common side effects.

Various nonpharmacological and pharmacological strategies for prevention of weight gain and metabolic disturbance have been tried in patients treated with SGAs. Pharmacological intervention such as amantadine, famotidine, fluoxetine, fluvoxamine, metformin, nizatidine, orlistat, ranitidine, reboxetine, sibutramine, topiramate, have been found to decrease weight gain induced by SGAs. Metformin is a hepatic-selective insulin sensitizer, it reduces weight, insulin resistance, and glycated haemoglobin (HbA_{1c}) in obese non diabetic adults. It is also known to decrease insulin resistance and abnormal glucose metabolism resulting from the treatment with SGAs like olanzapine.

In this 12 week randomized, open label study a total of 65 patients who satisfied the inclusion criteria were recruited, 59 completed the study. Dropout rate was 9.2%, similar findings were observed in two studies (7.3% and 7.2%) conducted by Wu RR et al. In the present study majority of patients were in the second and third decade of life, which is similar to other studies except in Baptista et al in which it was fourth decade, another study included mainly children and adolescents.[85-89] There were more number of females in our study, but in one study the gender distribution was equal in another study there was male predominance.[85,86] The mean duration of disease was nine months in our study as they visited the hospital after they had received other modalities of treatment except allopathy, in a study conducted by Wu RR et al it was seven years. Previous three studies had recruited patients suffering from schizophrenia, two studies by Baptista et al included patients with

schizophrenia, schizoaffective disorder and bipolar mania, we had patients with schizophrenia and bipolar mania.

In the present study there was increase in body weight by 10.3% in patients receiving olanzapine and 6.43% in olanzapine and metformin by the end of week 12. Studies conducted by Wu RR et al and Baptista T et al have shown similar findings.[85,86] But findings of two other studies indicate an increase of body weight with placebo whereas decrease with metformin.[87, 89] We also observed weight gain of more than 7% by week 12 in 86.2% of patients receiving olanzapine alone, but it was only 43.3% in olanzapine and metformin which was highly significant (Figure 7). Though addition of metformin did not significantly prevent mean weight gain but number of patients who had weight gain more than 7% was less when metformin was added along with olanzapine. In Wu RR et al study more than 7% weight gain was observed in 63.16% and 16.7% patients receiving placebo and metformin respectively.[85] These findings indicate that metformin may prevent weight gain induced by olanzapine, but there is a need for conducting a study for a longer duration and with more number of patients to establish the effect of metformin in olanzapine induced weight gain. There was weight gain in both the groups compared to baseline but relatively less weight gain in patients receiving metformin. This finding is similar to Baptista et al and Wu RR et al studies where the actual weight of the patients was taken into consideration and not the difference in weight gain.

The BMI increased in both the groups and there was a positive correlation between weight and BMI. Increase in this parameter was more with olanzapine than olanzapine plus metformin but it was not statistically significant (Figure 9). In two other studies it was observed that there was decrease in BMI in patients receiving metformin and increase with placebo.[87, 89]

In our study increase in the waist circumference and hip circumference in patients receiving metformin was less when compared to those receiving only olanzapine. This finding is in contrast with the Baptista T et al study where there was no difference in the waist circumference and hip circumference in patients receiving similar medications. In the present study there was an increase in the waist to hip ratio within group, but it was comparable between the two groups. Similar findings were also noted in Wu RR et al study.

In the present study there was a significant decrease in the fasting blood sugar at the end of 12 weeks in patients receiving additional metformin while there was no change in patients receiving only olanzapine. This finding can be utilized as a beneficial effect for patients receiving olanzapine who are at risk of developing metabolic syndrome and insulin resistance. Similar findings were also recorded in earlier studies.[90]

Addition of metformin did not affect the compliance. All the patients adhered to the treatment. Adverse drug reactions were analysed in patients who had received at least one dose of study drug. One patient had abdominal pain and constipation with metformin plus olanzapine, whereas severe weakness and somnolence was observed in one patient who received only olanzapine. Both these reactions were graded as probable according to WHO causality scale and they were withdrawn from the study.

Conclusion

CONCLUSION

- Schizophrenia is a severe form of mental illness, affecting either gender equally
- Most of the patients were in the age group of 25-45years and duration of illness was more than 9 months
- Baseline parameters like weight, height, BMI, waist circumference, hip circumference and fasting blood sugar values were comparable between groups
- Addition of metformin resulted in relatively less weight gain compared to patients who received only olanzapine
- Patients gaining clinically significant weight gain of more than 7% at week 8 and 12 were less when metformin was given along with olanzapine
- Percentage increase in weight from baseline to end of the study was 6.43% and 10.16% in patients who received metformin plus olanzapine and olanzapine alone respectively
- Although addition of metformin did not show a substantial reduction in weight, it is likely that a higher dose or longer duration of therapy may be required to observe such effects

Summary

SUMMARY

Schizophrenia is a severe form of mental illness and the treatment includes atypical or second generation antipsychotics (SGAs) which are associated with common side effects like weight gain and impairment in glucose metabolism. Metformin is an antidiabetic agent reduces weight, insulin resistance and abnormal glucose metabolism induced by SGAs like olanzapine.

In this study total of 65 patients clinically diagnosed with schizophrenia and bipolar mania as per ICD 10 were randomized and received olanzapine 10mg plus metformin 850mg or olanzapine 10mg once daily. Anthropometric measurements like weight, height and body mass index (BMI), waist circumference, hip circumference and waist to hip ratio were recorded at baseline, 4, 8 and 12 weeks. Fasting blood sugar was recorded only at baseline and week 12.

Ninety one percent of patients completed the 12 week study. There were 29 males and 36 females. Mean age was 51.03±11.47 and 49.83±10.60 in patients who received olanzapine plus metformin and olanzapine alone respectively. Weight, BMI, waist circumference, hip circumference and waist to hip ratio increased in both groups but it was relatively less in patients receiving metformin along with olanzapine. A clinically significant weight gain of more than 7% at week 12 was seen in less number of patients who received metformin along with olanzapine. Percentage increase in weight from baseline to end of the study was 6.43% and 10.16% in patients who received metformin plus olanzapine and olanzapine alone respectively.

There was a significant decrease in FBS level among patients who received olanzapine plus metformin at week 12 compared to baseline and also when compared to patients receiving olanzapine alone. One patient who received metformin plus

olanzapine had abdominal pain and constipation and one patient who received only olanzapine had severe weakness and somnolence. According to WHO causality assessment scale these reactions were graded as probable and they were withdrawn from the study.

In our study we observed that the weight gain in patients who received metformin plus olanzapine was relatively less compared to those who received olanzapine alone after 12 weeks of therapy, however this was insignificant. It is likely that a higher dose or longer duration of therapy with metformin may be required to observe a significant change in body weight.

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Annexures

PROFORMA

Serial No:

OP No: Date:

1. Name: 2. Age: 3. Gender:

4. Occupation: 5. Educational Status:

6. Address with phone no:

7. Complaints:

8. Family history:

9. Personal history: smoking/alcohol/drug intake/diabetes/hypertension/epilepsy

10. Diet history:

11. General physical examination:

12. Systemic examination:

13. Diagnosis:

Anthropometric measurements:

Parameters	Baseline	Week 4	Week 8	Week 12
Weight (kg)				
Height (cm)				
BMI (kg/m^2)				
Waist circumference (cm)				
Hip circumference (cm)				
Waist to Hip ratio				

Laboratory investigation:

Fasting blood glucose (mg/dl)	Baseline	Week 12

Adverse effects:

Adverse effects	Baseline	Week 4	Week 8	Week 12

Master chart