Introduction

Mental disorders are the greatest overall cause of disability. ***(Murray CJ, Lopez AD1996)***

Anti-psychotic drugs (APDs) are the most widely prescribed medications and are used frequently to control various mental disorders such as schizophrenia, bipolar disorder, dementia, major depression, Tourette's syndrome, eating disorders and even substance abuse. ***(Lambert T.2011)***

Unfortunately, APDs may cause some serious side-effects including extra-pyramidal and metabolic side-effects. Since typical APDs were introduced into clinics in the 1950s, their side-effects of increasing body weight have been reported, but have gained less attention because these drugs often have worse and problematic extrapyramidal side-effects. ***(Hasan A, et al., 2011).***

In the 1980s-1990s, clozapine, olanzapine and other atypical APDs with reduced extra-pyramidal side-effects were widely introduced into psychiatric clinics and currently form the first line of APD treatment. ***(Asenjo Lobos C, et al., 2010)***, Unfortunately, atypical APDs, particularly clozapine and olanzapine, cause serious metabolic side-effects, such as substantial weight gain, intra-abdominal obesity, hyperlipidemia,

insulin resistance, hyperglycemia, and type II diabetes mellitus (T2DM). ***(Correll CU et al., 2011)***

These adverse effects are a major risk for cardiovascular disease, stroke and premature death (by 20-30 years). ***(Stahl S, et al., 2009)***

Anti-psychotics may induce insulin resistance, glucose dysregulation, and even type II diabetes mellitus independent of weight gain and adiposity, There are also time-dependent changes for insulin and glucose dysregulation associated with anti-psychotic medication. ***(Deng, C. 2013).***

In addition to medical consequences, weight gain and obesity can lead to non-compliance with medication - a primary problem for the treatment of schizophrenia, since cessation of APD treatment dramatically (up to 5-times) increases the relapse rate for these patients. ***(Weiden PJ, et al., 2004).***

Aim of the Work

The aim of this study is to investigate whether BMI and some biochemical Parameters as Lipid profile and serum insulin add predictive information concerning risk for weight gain associated with treatment with atypical antipsychotics (AP).

Chapter (1)
Schizophrenia

Of all the major psychiatric syndromes, schizophrenia is perhaps the most Difficult to define and describe. This partly reflects the fact that, over the past century or more, widely divergent concepts have been held in different countries and by different people. Although there is now a greater consensus, substantial uncertainties remain. Indeed, schizophrenia remains the best example of the fundamental issues with which psychiatry continues tograpple−concepts of disease, classification, and etiology. Here, we start with an introduction to the major symptoms and other important clinical features.

Clinical features of schizophrenia:

These have classically been divided into two groupings:

1) Positive symptoms. These are delusions and hallucinations, the most florid and well-known types of symptom of schizophrenia. Particular types of delusion and hallucination (called first-rank symptoms) carry greater weight in the diagnosis and help distinguish schizophrenia from other psychotic disorders.

2) Negative symptoms. These are called "negative" symptoms because they reflect a loss of normal functioning. They are often listed as four As: alogia (decreased spontaneous speech), avolition (decreased motivation), affective flattening (lack of emotional expressivity, but not depression) and anhedonia. ***(Marder & Galderisi, 2017)***

In recent years, other features of schizophrenia have been grouped together in two further categories:

- Behavioral disorganization. This includes formal thought disorder (abnormalities in the flow and sequence of thoughts; in the past this was often considered as a positive symptom) as well as inappropriate affect and bizarre behavior.
- Cognitive symptoms. The extent and significance of attentional and memory impairments in schizophrenia, discussed below, has been increasingly recognized, and hence they are now often considered as a separate symptom category.

The predominant symptoms differ between acute schizophrenia and chronic schizophrenia, and the further description of the clinical syndrome is divided on this basis.

Briefly, the acute syndrome is dominated by positive symptoms, with subtypes of acute schizophrenia classically recognized based upon the relative prominence of different positive symptoms. Many patients recover from the acute illness, but progression to the chronic syndrome is also common. Chronic schizophrenia is characterized by negative symptoms; once the chronic syndrome is established, few patients recover completely.

Note, however, that the acute versus chronic distinction is an oversimplification; all features of schizophrenia can occur, and co-occur, at any phase of the illness. ***(Green, 2018)***

Antipsychotics:

This term is applied to drugs that reduce psychomotor excitement and control symptoms of psychosis. Alternative terms for these agents are neuroleptics and major tranquillizers. None of these names is wholly satisfactory.

"Neuroleptic" refers to the side effects rather than to the therapeutic effects of the drugs, and ‘major tranquillizer’ does not refer to the most important clinical action. The term ‘antipsychotic’ is used here because it appears in the British National Formulary.

The main therapeutic uses of antipsychotic drugs are to reduce Hallucinations, delusions, agitation, and psychomotor excitement in Schizophrenia, mania, or psychosis secondary to a medical condition. The drugs are also used prophylactically to prevent relapses of schizophrenia and other psychoses. The introduction of chlorpromazine in 1952 led to Substantial improvements in the treatment of schizophrenia, and paved the way to the discovery of the many psychotropic drugs that are now available.

Antipsychotic drugs share the property of blocking dopamine receptors. This may account for their therapeutic action, a suggestion that is supported by the close relationship between their potency in blocking dopaminergic receptors in vitro, and their therapeutic strength.

Imaging studies show that acute psychosis is associated with increased dopamine release in striate regions, and that the extent of this increase correlates with the subsequent therapeutic effect of antipsychotic drugs.

A persuasive formulation of antipsychotic drug action suggests that these agents block the ability of increased dopamine release to attribute abnormal salience to irrelevant stimuli. ***(Shitij Kapur, 2003)***

Dopamine receptors are of several subtypes. It is the D2 receptor that is critical for antipsychotic action, and all licensed drugs in the category are antagonists at this receptor, with varying affinities for the D2 subtype.

PET studies suggest that an antipsychotic effect is obtained when D2-receptor occupancy lies in the range 60–70%. Higher levels are associated with extra pyramidal movement disorders and hyperprolactinaemia, but not with greater efficacy, other side effects are attributable to binding to a variety of other receptors. ***(S Kapur, Zipursky, & Remington, 1999)***

Distinction between typical and atypical antipsychotic drugs:

The term atypical antipsychotic agent was introduced to distinguish the newer antipsychotic drugs from conventional typical agents, such as chlorpromazine and haloperidol. An alternative term is second generation.

Although the definition of the term 'atypical' varies in the literature, a fundamental property of an atypical antipsychotic is its ability to produce an antipsychotic effect without causing extrapyramidal side effects. This definition is problematic, not least because antipsychotics do not fall

clearly into two classes in this respect, but lie along a spectrum. For example, low potency conventional antipsychotic drugs such as chlorpromazine have a relatively low risk of producing extrapyramidal symptoms when prescribed at modest dosages; conversely, extra pyramidal side effects can also occur with the atypical antipsychotic risperidone. However, it is true to say that atypical antipsychotic agents have a lower likelihood of causing extrapyramidal side effects within their usual therapeutic range. In addition, the risk of tardive dyskinesia appears to be lower with the newer antipsychotic drugs. ***(Correll, Leucht, & Kane, 2004)***

Another property that is sometimes attributed to atypical antipsychotic Drugs is improved efficacy relative to typical agents. Although this is true in terms of positive psychotic symptoms for the prototypic atypical antipsychotic, clozapine, it is not clear how far more recently developed compounds meet this exacting criterion.

A multiple treatments meta-analysis of placebo-controlled trials showed that evidence in this respect is strongest for amisulpride, olanzapine, and risperidone ***(Leucht et al., 2013).***

However, pragmatic trials have so far failed to demonstrate important therapeutic differences between conventional and newer antipsychotic drugs, and even clozapine does not have proven efficacy against negative or cognitive symptoms. For these and other reasons, most authorities now believe that the terms "atypical" and "typical" antipsychotic are not useful, and that attention is better directed towards the pharmacological properties of individual drugs and their associated therapeutic profile. ***(Leucht et al., 2013)***

Pharmacology of typical (conventional) antipsychotics:

All of these drugs are effective dopamine-receptor antagonists, but many possess additional pharmacological properties that influence their adverse effect profile.

Phenothiazines:

Chlorpromazine is the prototypic phenothiazine. It antagonizes α1- adrenoceptors, histamine H1-receptors, and muscarinic cholinergic receptors.

Blockade of α1-adrenoceptors and histamine H1-receptors gives chlorpromazine a sedating profile, while α1-adrenoceptor blockade also causes hypotension. The

anticholinergic activity may cause dry mouth, urinary difficulties, and constipation, while on the other hand offsetting the liability to cause extrapyramidal side effects. In contrast to chlorpromazine, piperazine compounds such as trifluoperazine and fluphenazine are more selective dopamine-receptor antagonists, and are therefore less sedating but more likely to cause extrapyramidal effects.

Thioxanthenes and butyrophenones:

Thioxanthenes such as flupenthixol and clopenthixol are similar in structureto the phenothiazines. The therapeutic effects are similar to those of the piperazine group. Butyrophenones such as haloperidol have a different structure but are clinically similar to the thioxanthenes. They are potent dopamine-receptor antagonists, with few effects at other neurotransmitter receptors. They are not sedating, but have a high propensity to cause extrapyramidal side effects.

Pharmacology of atypical antipsychotic drugs:

Selective D2-receptor antagonists:

Atypical antipsychotic drugs have a diverse pharmacology, but currently two main groupings can be discerned. On the one hand are substituted benzamine's such as sulpiride and amisulpride. These drugs are highly selective

D2-receptor antagonists which, for reasons that are not well understood, seem less likely to produce extrapyramidal movement disorders.

They also lack sedative and anticholinergic properties. However, they do cause a substantial increase in plasma prolactin.

5-HT2-D2-receptor antagonists:

The other major group of atypical antipsychotic drugs possesses 5-HT2-receptor-antagonist properties. In other aspects−for example, potency of dopamine D2-receptor blockade, these drugs differ significantly from one another. ***(Leslie Citrome, 2013).***

Risperidone is a potent antagonist at both 5-HT2 receptors and dopamine D2 receptors. It also possesses α1-adrenoceptor-blocking properties, which can cause mild sedation and hypotension. Paliperidone is an active metabolite of risperidone and has very similar pharmacological properties when given orally.

Olanzapine is a slightly weaker D2-receptor antagonist than risperidone, but has anticholinergic and powerful histamine H1-receptor-blocking activity.

This gives it strong sedating effects. Quetiapine is also a histamine H1-receptor antagonist; it has modest 5-HT2-receptor-antagonist effects, and rather weaker D2-receptor-antagonist properties. It has a low propensity tocause movement disorders and, like olanzapine, is highly sedating.

Lurasidone is a potent 5-HT2 and D2 receptor antagonist. It binds only weakly to histamine H1 receptors, which makes it less likely to cause weightgain and sedation than olanzapine or quetiapine. Asenapine binds potently to5-HT2 receptors. It also binds significantly to D2 receptors, as well as to arrange of other 5-HT receptors and the alpha-2-adrenoreceptor, but the contribution of these latter properties to its therapeutic effect is unclear. Inthe UK and Europe, asenapine is licensed for the treatment of mania but not schizophrenia. It requires sublingual administration.

Sertindole is a potent 5-HT2-receptor antagonist with weak D2-receptorantagonisteffects. It causes clinically significant effects on the QT interval in the electrocardiogram, and its use is currently suspended. Ziprasidone is another 5-HT2 and D2-receptor antagonist, which differs from the other 5-HT2/D2-receptor antagonists described here, because it also binds to 5-HT1Areceptors and

is a noradrenaline reuptake inhibitor. Somnolence anddizziness are common side effects of ziprasidone, and it causes relatively little weight gain. It has a tendency to increase the QT interval, and has not been licensed in the UK. Aripiprazole is a partial dopamine agonist that also has 5-HT2-receptor-blocking and 5-HT1A-agonist properties. It has anactivating profile and pro-dopaminergic side effects such as insomnia, nausea, and vomiting. It is less likely to cause weight gain than quetiapine or olanzapine.

To some extent these latter drugs were designed to reproduce the pharmacological profile of clozapine, which was the first antipsychotic agent to show definite benefit in the treatment of patients whose psychotic symptoms had failed to respond to conventional agents. In addition, clozapine has a low liability to cause movement disorders, and is therefore usually regarded as the prototypic atypical antipsychotic drug ***(J. Kane, Honigfeld, Singer, & Meltzer, 1988).***

Clozapine is a weak dopamine D2-receptor antagonist but has a high affinity for 5-HT2receptors. It also binds to a variety of other neurotransmitter receptors, including

histamine H1, α1-adrenergic and muscarinic cholinergic receptors ***(Meltzer, 2004).***

Various studies have attempted to define a therapeutic plasma range for clozapine, with inconsistent results. A reasonable compromise between efficacy and safety is 350-500 μg/l. Above 600 μg/l the risk of seizures increases significantly. The pharmacological basis for the increased efficacy of clozapine is not well understood. However, it is clear that the use of clozapine is associated with a significant risk of leucopenia, which restricts its use to patients who do not respond to or who are intolerant of other antipsychotic drugs.

Depot antipsychotic drugs:

Slow-release preparations are used for patients who need to take antipsychotic medication to prevent relapse but cannot be relied upon to take it regularly. These "depot" preparations include the esters of conventional antipsychotic drugs such as fluphenazinedecanoate, flupenthixoldecanoate, zuclopenthixoldecanoate, haloperidol decanoate, and pipotiazine palpitate.

All are given intramuscularly in an oily medium. Zuclopenthixol acetate reaches peak plasma levels within 1-