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A Cross Sectional Study Of Atypical Antipsychotics Induced Weight Gain And Metabolic Syndrome (Mets)

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ABSTRACT:
A typical antipsychotics (AAPs) are commonly used drug group in psychiatric practice. They treat both positive and negative symptoms of psychiatric spectrum disorders effectively without extra pyramidal side effects.
Aim: The study aimed to investigate the frequency and predictors of atypical antipsychotics (AAPs) induced weight gain and metabolic syndrome (METs).
Objective:
Primary objective: To investigate the frequency, causality, and severity of AAPs induced weight gain and metabolic syndrome using the Naranjo's scale, WHO criteria, and Hartwig Severity assessment
Secondary objective: To investigate the predictors of AAPs induced weight gain and metabolic syndrome
Methodology: This was a hospital based cross-sectional study conducted in Psychiatry Department at Karpagam Hospital, Coimbatore for a period of 6 months. Patient of any gender, any age group, a patient diagnosed with psychotic spectrum disorder as per the ICD diagnostic criteria, patients prescribed with atypical antipsychotics with complete clinical data and patients with anthropometric data such as height, weight, BMI before and after atypical atypical antipsychotic were included in the study. GraphPad Prism 9.4.1 version was used to perform the descriptive statistical analysis and univariate analysis.
Keywords: Atypical antipsychotic drugs, AAPs, metabolic syndrome, cross sectional study, weight gain

I. INTRODUCTION

Psychosis is a symptom, not an illness and it can be triggered by a mental illness, a physical injury or illness, substance abuse, and extreme stress or trauma. Antipsychotics Drugs (APDs) also known as neuroleptics, that act as a powerful tranquilizers to reduce the symptoms of Psychosis intellectual disorders **(T.S Kishiet et al 2021).** Five important intellectual illnesses such as autism, interest deficit hyperactivity sickness, bipolar sickness, important depressive sickness, and schizophrenia, are comes under psychiatric spectrum disorder (PSD).

APDs are the only remedy for schizophrenia and various psychotic disorders. They have historically been classified as first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). The FGAs are dopamine receptor antagonists (DRA) and are referred to as "traditional antipsychotics". They encompass phenothiazines(trifluoperazine, perphenazine,acetophenazine, triflupromazine,mesoridazine) butyrophenones(haloperidol), thioxanthene's,(thiothixene chlorprothixene) dibenzoazepine's loxapine, dihydroindoles (molindone), and diphenyl butyl piperidines (pimozide). SGAs are serotonin dopamine antagonists and also are referred to as "peculiar antipsychotics". The Food and Drug Administration (FDA) has authorized 12 peculiar antipsychotics as of the year 2016. They are risperidone, olanzapine, quetiapine, Ziprasidone, Paliperidone, asnapine, Lurasidone, iloperidone, cariprazine,brexpiprazole, and clozapine, (**K.Y Lee et al 2020; A.T ˙ Lambert et al 2018 & A.B Aleem Akbar et al 2021).**

Adverse drug effects of FGAs associated with extrapyramidal and antipsychotic effects such as dry mouth, constipation, and urinary retention are not unusual. Haloperidol can be the reason for odd coronary heart rhythm, and ventricular arrhythmia; others (FGAs) can be the reason for prolongation of QTC interval, extended atrial and ventricular contraction, and different cardiac conduction abnormalities.

Atypical antipsychotics (AAPs) are the most commonly used antipsychotic medications in psychiatric practice because typical antipsychotics are associated with poor efficacy against negative symptoms and are associated with unwanted extrapyramidal symptoms such as bizarre body movements like parkinsonism, rigidity, and tremors. On the other hand even at the higher doses Particularly at higher doses the less incidence of atypical antipsychotics have a remarkably lower

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incidence of extrapyramidal signs and are replaced with atypical antipsychotics with significantly reduce both positive and negative symptoms. However, the spectrum of ADRs, such as weight gain and gastrointestinal upset, is common with AAPs

Adverse drug effects of APPs are associated with tremendous weight gain and metabolic syndrome. The SGAs have a reduced chance of extrapyramidal aspect outcomes in comparison to first-generation antipsychotics. For example, risperidone is associated with dizziness, anxiety, sedation, and extrapyramidal aspect outcomes. Paliperidone can cause temperature sensitivity to warm temperatures and QTC prolongation. Olanzapine is associated with higher incidence related maximum regularly to weight gain, expanded appetite, and somnolence. Quetiapine is the least probable reason extrapyramidal aspect outcomes of quetiapine are somnolence. SGAs can contribute to weight gain.

A meta-analysis provided an estimate of the mean weight gain in patients receiving standard doses of antipsychotics over 10 weeks: 4.45 kg with clozapine, 4.15 kg with olanzapine, 2.92 kg with sertindole, 2.10 kg with risperidone, and 0.04 kg with ziprasidone **(Ojagbemi. J et al 2021)**

Metabolic syndrome is a condition that includes a cluster of risk factors specific to cardiovascular disease. These factors include obesity, high blood pressure, impaired fasting glucose, high triglyceride levels, and low HDL cholesterol level. Metabolic syndrome is mainly diagnosed by the following five criteria, waist circumference of 40 inches (men) and 35 inches (women), blood pressure of 130/85 mg/dl, triglyceride level of 150mg/dl, and high-density lipoprotein. Second-generation antipsychotics (SGAs) are known to increase cardiovascular risk through several physiological mechanisms, including insulin resistance, hepatic steatosis, hyperphagia, and accelerated weight gain. Atypical Antipsychotic-induced weight gain is a major management problem. It has been shown that weight gain and obesity lead to increased cardiovascular and cerebrovascular morbidity and mortality & reduced quality of life **(Hubertus Himmerich et al 2020)**

Significance of the study

Atypical antipsychotic medications are the most commonly used antipsychotic medications in psychiatric practice because typical antipsychotics are associated with poor efficacy against negative symptoms and are associated with unwanted extrapyramidal signs and symptoms. Particularly at higher doses, these typical antipsychotics commonly show bizarre body movements like parkinsonism, rigidity, and tremors. Atypical antipsychotics have a remarkably lower incidence of EPS and significantly reduce both positive and negative symptoms. However, the spectrum of ADRs, such as weight gain and gastrointestinal upset. (**Meenakshi.T.2019)**

Over the last few years, atypical antipsychotics have been increasingly used in the pharmacological treatment of schizophrenia and other related psychotic disorders. These agents improve quality of life, have better medication compliance, and also decrease suicidal tendencies and depression in these patients. One of the studies from the US showed more than 25% of male patients with at least one claim for an atypical antipsychotic were aged 9 years and younger. Prevalence peaked at 594.3 per 100 000 patients among male patients aged 10 to 14 years and at 291.0 per 100 000 patients among female patients aged 15 to 19 years. Risperidone was the most commonly used atypical antipsychotic among both male and female patients**. (Piprava.K et al 2011**.)

The adverse effects of AAPs include hypotension, seizures, weight gain, increased risk of diabetes mellitus, and hyperlipidemia. Weight gain is considered clinically significant if it exceeds 7% of the initial weight after 10 weeks. Studies have shown that observed weight gain with Olanzapine and risperidone accounted for 15.53% of ADR. Weight gain in older patients (> 60 years) treated with atypical antipsychotics is lower than that seen in younger adults. One of the South Indian studies has shown that out of 50 patients
subjected to the study, weight gain was observed in 26 patients (52%). The second common adverse drug reaction was found to be tremor, which was observed in 25 patients (50%). Adverse reactions to antipsychotics were observed in the patients. Second-generation antipsychotics, clozapine, and olanzapine are known to cause weight gain. Olanzapine also impairs glucose regulation and causes dyslipidemia, which leads to an increase in body fat. Weight gain has also been linked to an increase in serum leptin levels**. (Meenaka. K 2017).**

Clozapine has an average body weight gain represented by a range from 2.3 to 16.2 kg in the 27 to 78% of patients treated with clozapine for a duration of 16 weeks to 24 months. Increases in body weight of 1.9 to 11.8 kg have been reported in patients taking olanzapine, with a prevalence rate of 41 to 94%**(Sarumathyetal . L et al 2019.,)**

.Second-generation antipsychotics (SGAs) are known to increase cardiovascular risk through several physiological mechanisms, including insulin resistance, hepatic steatosis, hyperphagia, and

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accelerated weight gain. Atypical antipsychotic-induced weight gain is a major management problem. It has been shown that weight gain and obesity lead to increased cardiovascular and cerebrovascular morbidity and mortality and reduced quality of life**. (Madhubhashinee & Dayabandara. M et al 2017).;**

Though many studies in India have studied the prevalence of AAPs-induced WG or other ADRs, very few studies have focused on the predictors of AAPs-induced weight gain. we aim to investigate the frequency & predictors of AAPs induced weight gain & METS through a hospital-based cross-sectional studyStudy Setting

The study was conducted in the Psychiatry Department, at Karpagam Hospital. The study was conducted as a hospital-based cross-sectional study over 6 months. The protocol was approved by the independent ethics committee (IEC) of the Karpagam Faculty of Medical Science and Research and the approved reference number is IHEC/273/KCOP/09/2022. The researchers made sure that the study was carried out as per the principles of the Declaration of Helsinki. The sample size was calculated using Cochran's formula.

Study Criteria

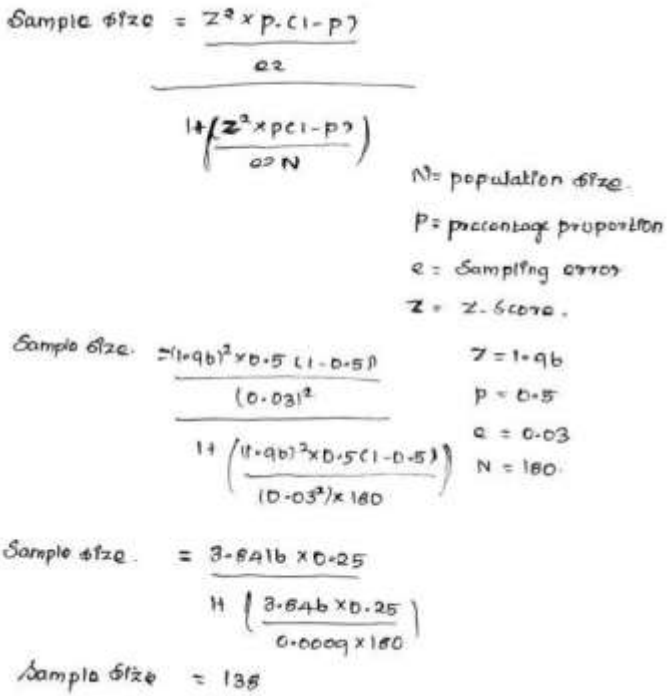
Patients of any gender, any age group, a patient diagnosed with psychiapric illness.

Scales Used

In this study Naranjo's scale was used to assess the causality of AAPs induced weight gain and metabolic syndrome and the score was calculated as definite > 9, probable from 5 to 8, possible from 1 to 4, and doubtful as 0. Patients who scored probably (5 to 8) were included for further analysis. The severity of AAPs-induced weight gain and METs was assessed using Hartwig Severity Assessment Scale. The WHO criteria were used to confirm the AAPs induced metabolic syndrome (**Albert KG et al 1999., Balkau..G et al 1999**. Adult treatment panel III, 2001)

Sample size

BMI before and after atypical antipsychotic were included in the study. On the other hand, pregnant women, breastfeeding women, patients with eating disorders, and patients with a history of hypertension and diabetes were excluded. Patients who scored more than 20 data,(abnormal eating behavior) on the dietary history assessment scale were excluded as well. and patients with anthropometric data such as height, weight, criteria, patients prescribed with atypical antipsychotics with complete clinical spectrum disorder as per the ICD diagnostic



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Statistical Analysis

GraphPad Prism version 9.4.1 was used to perform the the descriptive statical analysis and univariate analysis chi^2 and fisher exact test was used analyse the predictors of AAPs induced weight gain & MET

This study included overall 75 patients, 45 patients were recruited retrospectively 30 patients were recruited prospectively. Of a total of 75 patients, 70% of the patients were in the age range of 1- 60 and the remaining 30% of patients were in the age of above 60. The percentage data showed more no of patients in the adult category, however, there was not much difference in these groups (p=0.07).
Male preponderance was seen in our study, out of 75 patients 60% of patients were males and this difference was statistically significant (p=0.05). There was not much difference between smokers and non-smokers (p=0.47),

Table 5.1 Patient Demographic Characteristics

Parameters	Retrospective n= 45 (%)	Prospective n=30 (%)	Total 75	p value
Age 1-60 >60	 28 (62%) 17 (37%)	 25 (83%) 05 (16%)	 53 (70%) 22 (29%)	0.07
Gender Male Female	 23 (51%) 22 (48%)	 22(80%) 8(20%)	 45 (60%) 30 (40%)	0.05
Smoking Yes No	 12 (26%) 28 (62%)	 14 (46%) 16 (53%)	 26 (34%) 28 (37%)	0.47
Alcohol Yes No	 15 (33%) 30 (66%)	 13 (43%) 17(56%)	 15 (20%) 47(62%)	0.46
Surgery Yes No	 0 45 (100%)	 0 30 (100%)	 75 (100%)	-
Past Medical History Yes No	 25 (55%) 20 (44%)	 20 (66%) 10 (33%)	 45 (60%) 30 (40%)	0.0003
Diagnosis (ICD10) Severe psychological problem (SPP) Common psychological problem (CPP)	 24(53%) 21(46%)	 19 (63%) 11 (36%)	 43 (57%) 32 (42%)	-
AAPS Olanzapine Clozapine Risperidone Risperidone+Trihexyphenidyl Ola/Risp	 19(42%) 5(11%) 5(11%) 6(13%) 10(23%)	 7(23%) 3(10%) 5(16%) 11(36%) 4(13%)	 26 (34%) 8 (10%) 10 (13%) 17 (22%) 14 (18%)	-
ADR Weight Gain MetabolicSyndrome Weight /METS	 22(48%) 10(23%) 13(28%)	 13 (43%) 10(33%) 7(23%)	 35 (46%) 20 (26%) 20 (26%)	-

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Table 5. 2 Anthropometric Data

Parameters	Retrospective N=45		Prospective N=30		Total N=75	
	Before AAPs	After AAPs	Before AAPs	After AAPs	Before AAPs	After AAPs
Weight						
40-50kg	6(13.3%)	4(8.8%)	1	1	7 (9.3%)	5 (6.6%)
50-60kg	11(24.4%)	7(15%)	8(26.6%)	7(23%)	19 (25%)	14 (18%)
60-70kg	18(40%)	19(42.2%)	9 (30%)	6 (20%)	27 (36%)	25 (33%)
>70kg	10(22%)	15(33%)	12(40%)	15(50%)	22 (29%)	30 (40%)
BMI						
Under Weight	2 (4.4%)	1 (2.2%)	0	0	2 (2.6%)	1(1.3%)
Normal	29	28 (62%)	13(43.3%)	13(43%)	42 (56%)	41(54%)
Over Weight	(64.4%)	16 (35%)	11(36%)	12(40%)	25 (33%)	28 (37%)
Obesity	14	0	6(20%)	5(16%)	6 (8%)	6 (6.6%)
	(31.1%)					
	0					
Waist Circumference						
Females	-	-	4 (13%)	8 (26%)		
Waist	-	-				
=>0.85						
>88cm	-		8 (26%)	12 (40%)		
Males						
Waist=>0.90						
> 102cm						
Thigh Circumference	-	-	4 (13%)	8 (26%)		
Female (51cm)	-	-	8 (26%)	12 (40%)		
Male (54cm)						

AAPs-Atypical antipsychotics drugs, BMI- Body mass index

5.3 AAPs induced metabolic syndrome

BP, lipid profile, and blood glucose test data were obtained before and after the AAPs introduction. Before AAPs treatment, 38 patients were having a systolic BP of 140mm/hg and this frequency has increased from 38 to 65 patients. Likewise, 40 patients had a diastolic BP of 90mm/Hg before AAP treatment, followed by this number increased to 59 and these differences were found to be statistically significant (p=<0.0001). Though the percentage data has shown lipid profile abnormality after AAPs treatment, it was not statistically significant (TG-p=0.736, HDL-p=0.243, LDL-p=0.508). Likewise, the percentage data of blood glucose tests have shown that more patients were with abnormal glucose levels after introducing

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AAPs, but statistically, these differences were not significant.

Table 5. 3 Atypical Antipsychotics Induced Metabolic Syndrome (WHO Med)

Parameters	Retrospective N=45		Prospective N=30		Total		P value
BP Systole	Before AAPs	After AAPs	Before AAPs	After AAPs	Before AAPs	After AAPs	
>140mm\Hg	28 (62%)	42 (93%)	10(33%)	23(76%)	38 (50%)	65 (86%)	<0.0001
Diastole >90mm\Hg	26 (57%)	38 (84%)	14 (46%)	21(70%)	40 (53%)	59 (78%)	0.0018
Lipid Profile							
Tg> 1.7mmol/L	19 (42%)	22(48%)	8(26%)	13(43%)	27 (36%)	30 (40%)	0.736
HDL>1.29mmol/L	20 (44%)	23(51%)	9(30%)	11(36%)	26 (34%)	34 (45%	0.243
LDL>3.3mmol/L	20 (44%)				29 (38%)	34 (45%)	0.508
Blood Glucose Test	0	0	0	0	0	0	
HBA1C	15 (33%)	20(44%)	6(20%)	8(26%)	21 (28%)	28 (37%)	0.28
Fbs>5.6mmol/L	18 (40%)	25(55%)	5(16%)	3(20%)	23 (30%)	28 (3\%)	0.482
Rbs>7.8mmol/L							

5.6 Atypical Antipsychotics induced Weight Gain/ Metabolic syndrome

Among all the AAPs more weight gain cases were reported with olanzapine, and risperidone either as monotherapy or in combination therapy. Likewise among 20 patients who have exhibited the symptoms of metabolic syndrome, 70% of the patients reported for risperidone and olanzapine. The same kind of frequency pattern was seen with AAPs induced both weight gain and metabolic syndrome. For instance, among 20 patients with both weight gain and metabolic syndrome, 75% were prescribed risperidone and olanzapine. Causality, severity, and dietary history assessment scores were listed in Table no 7.

Table 5.4 Atypical Antipsychotics Induced Weight Gain

Drugs	Retrospective N=22	Prospective N=13	Total N=35
Risperidone	8 (36%)	3 (23%)	11 (31%)
Olanzapine	7 (40%)	7 (38%)	14 (40%)
Clozapine	3 (13.6%)	0	3 (8.5%)
Ola/Res/	2 (9%)	1(7.6%)	3 (8.5%)
Risperidone+trihexyphenidyl	2 (9%)	2(15%)	4 (11%)

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Table 5. 5 Atypical Antipsychotics induced Metabolic syndrome

Drugs	Retrospective N=10	Prospective N=10	Total N=20
Risperidone Olanzapine Clozapine	4 (40%)	3(30%)	7 (35%)
Riscon forte	4 (40%)	3(30%)	7 (35%)
	2 (20%)	1(10%)	3 (15%)
	0	4(40%)	4 (20%)

Table 5. 6 Atypical Antipsychotics induced WG/Metabolic syndrome

Drugs	**Retrospective N=13**	**Prospective N=7**	**Total N=20**
Risperidone Olanzapine Clozapine	3 (30%)	1 (10%)	4 (20%)
Riscon forte	5 (50%)	4 (40%)	9 (45%)
	2 (20%)	0	2 (10%)
	3 (30%)	2 (20%)	5 (25%)

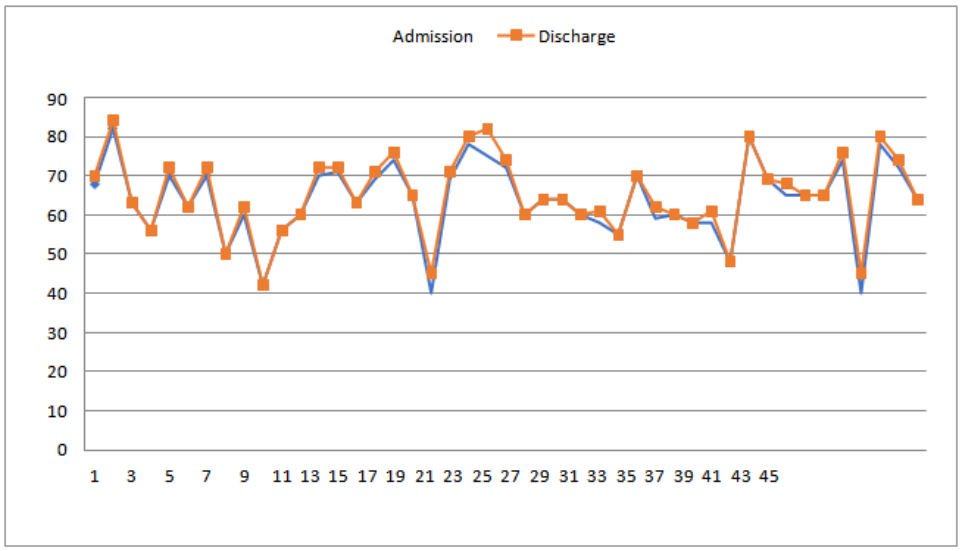

Figure 5.1. WG difference between admission and discharge for the retrospective data

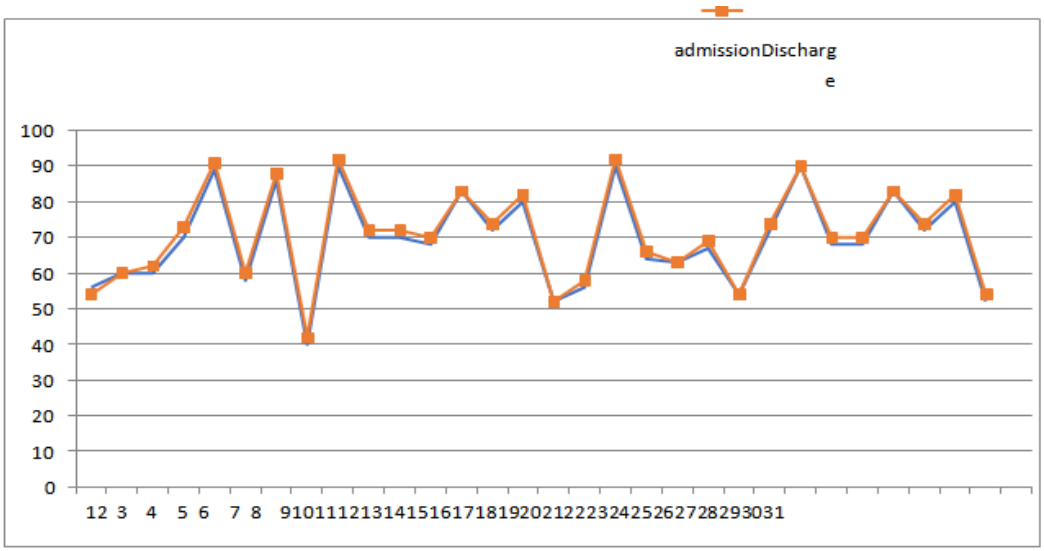

Figure 5.2. WG difference between admission and discharge for the prospective data

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Table 5.7 Causality, Severity, and Dietary History Assessment Score

Parameters	Retrospective N=45	Prospective N=30	Total N=75
Naranjo's scale Definite>9 Probable 5-8			
Possible 1-4	28 (62%)	18 (60%)	46 (61%)
Doubtful 0	17 (37%)	12 (40%)	29 (38%)
	-	-	-
Hartwig severity Scale			
Level 1	23 (51%)	15 (50%)	38 (50%)
Level 2	12 (26%)	7 (23%)	19 (25%)
Level 3	10 (22%)	8 (26%)	18 (24%)
Level 4	-	-	-
Level 5	-	- 17(56%)	-
Level 6		13 (43%)	
	-		17 (45%)
Diet history Score			
1-14 (NEH)	-		13 (43%)
15-20 (moderate AEH)			

NEH-Non eating habits, AEH-Abnormal eating habits.

Figures 5.1 and 5.2 have shown the weight difference between the date of admission and date of discharge for the retrospective and prospective data respectively. This study has assessed the causality between ADRs and AAPs. The calculated score was in the category of probable (60%) and possible (38%). Almost 50% of the ADRs were in the severity scale of 2 and 3, the remaining 50% was in level 1 severity. The dietary history was assessed using a customized questionnaire which was prepared from the original NIH dietary history questionnaire. Patients who were having normal eating behavior had scored within 1-14 and patients who scored more numbers exhibited a moderate level of abnormal behavior. In this study, 17 patients scored for normal eating behavior, and the remaining 13 patients were with a moderate level of abnormal eating behavior.

Table 5. 8 Predictors of AAPs-induced WG/METs

Parameters	OR	95% CI	P value
Age (1-60 -Adults)	1.952	0.643-5.607	0.25
Gender (Male)	1.548	(0.507-4.108)	0.44
Smoking (Yes)	0.378	0.128-1.14	0.08
Alcohol (Yes)	0.366	0.125-0.99	0.06
Past Medical History (Yes)	1.167	0.382-3.112	0.79
Dietary Assessment Score (1-14)	0.740	0.143-3.361	>0.99
Diagnosis (SPP)	0.583	0.208-1.627	0.32

SPP-Severe psychological problems

Table 5.8 showed the predictors of AAPs-induced WG and METs. None of the factors were found to be predictors of AAPs-induced WG/METs. However, based on OR value, age (1- 60), gender (males) and past medical history (yes) can be considered as predictors.

II. RESULTS:

Out of 75 patients, 45 and 30 patients were recruited for this study in a retrospective and

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prospective way respectively. Almost 50% of the patients reported with weight gain, 20 patients reported with metabolic syndrome alone and twenty patients were reported with both weight gain and metabolic Syndrome. Olanzepine and Risperidone were the most commonly prescribed AAPs as monotherapy and in combination therapy. Odds ratio of age (1- 60) (OR=1.952, 95% CI -0.643-5.607, p=0.25), gender (males) (OR=1.548, 95% CI -0.507-4.108, p=0.44), and past medical history (yes) (OR=1.167, 95% CI -0.038-3.112, p=0.79) were showing positive results. Hence these factors could be the predictors of AAPS induced weight gain and metabolic syndrome.

III. CONCLUSION:

Among all AAPs, Olanzapine and risperidone were the most common drugs found in the WG and METs patients. Odds Ratio for the age range 1-60, males, and past medical history was found to be higher. This study must be continued prospectively with a larger sample size to increase the statistical power of this work in future.