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EVALUATION OF LIPID PROFILE IN PATIENTS ON ATYPICAL ANTI PSYCHOTIC MEDIACTIONS

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ABSTRACT
The use of atypical antipsychotics was reported to cause the variation in the lipid levels, i.e. triglyceride levels (TG), cholesterol levels (TC), LDL and HDL levels in the patient which is a precursor to many cardiac disorders. The aim of the study is to assess the variations of lipid levels in patients associated with atypical antipsychotics. This study is designed as a Prospective Observational Study (Follow-Up study) which was carried out in Psychiatric department of Rajiv Gandhi Institute of Medical Science, Kadapa and MNR Hospital, Hyderabad simultaneously for a period of 9 months. The patient's base-line values of lipid profiles (TG, TC, HDL and LDL) were recorded and regular follow-ups were done for every 4 weeks until 4 months and finally the variations associated with atypical antipsychotics were assessed. We have recruited 46 patients based on the eligibility criteria. The baseline values were normal and at end of the study the lipid profiles of patients were altered, i.e. increased values total cholesterol, triglyceride levels and there were no significant changes in the HDL and LDL levels with the use of atypical antipsychotics. The drugs tends to cause variations in the lipid levels of patients fall in the order, OLANZAPINE (10mg) > CLOZAPINE (10mg) + RISPERIDONE (3mg) > RISPERIDONE (3mg) > OLANZAPINE (5mg) > OLANZAPINE (10mg) + CLOZAPINE (50mg) > RISPERIDONE (2mg). Concluding this research that the AAPs are producing an increased incidence of hyperlipidemia in the blood which leads to cardiac complications, so the management of psychiatric disorders should be multidisciplinary including psychiatrist, general physician, cardiologist and paramedical staff.

KEYWORD: hyperlipidemia, LDL and HDL.

INTRODUCTION
Hyperlipidemia is an elevation of one or more fat proteins in the blood. It is commonly referred to as high cholesterol. One-third of American adults have it, only 1 in 3 have it under control, and having hyperlipidemia doubles the risk of developing heart disease**.** Lipid is the scientific term for fats in the blood. At proper levels, lipids perform important functions in your body, but can cause health problems if they are present in excess. The term hyperlipidemia means high lipid levels.[1] Unhealthy lifestyle including lack of exercise,[2] poor diet,[3] and cigarette smoking[4] are few factors for hyperlipideia. Inaddition, genetic risk[5] and the use of antipsychotic drugs are also the causes.

Hyperlipidemia is too much cholesterol in the blood. Cholesterol is a waxy, fat protein manufactured by the liver and is essential for healthy cell membranes, hormone production, and vitamin storage. Even the brain depends on cholesterol for proper functioning. Cholesterol becomes a problem when too much of the bad kind is produced or ingested through regular eating of unhealthy foods[6]

Cholesterol is carried through the blood to cells by lipoproteins that are either low density (LDL) or high density (HDL). Think of the lipoprotein as the vehicle and cholesterol as the passenger. HDL is the good lipoprotein because it carries extra cholesterol back to the liver where it can be eliminated. LDL is bad, as it will build up excess cholesterol in the blood. Triglycerides, a type of fat in the blood, are different from cholesterol, but because of their strong association with heart disease, triglycerides are measured as well. Often it is both the LDL and triglycerides that are elevated in hyperlipidemia.[6]

MORTALITY OF PSYCHOTIC ILLNESSES
Several studies have reported that there is increased mortality rate in patients with schizophrenia. The US Food and Drug Administration also made aware to the health care practitioners about the increased risk of

mortality in elderly patients taking typical or atypical antipsychotic drugs.

MECHANISMS OF ATYPICAL ANTIPSYCOTICS:

1. Blocks M_3 muscarinic acetylcholine receptors which are responsible for regulating the release of insulin.
2. Inappropriately changing the body's energy sources from carbohydrates to lipids.
3. Causing weight gain by antagonizing the histamine H_1 and serotonin 5-HT_{2C} receptors.

Some more possible mechanisms side effects of antipsychotics are suggested:

Dyslipidemia

Dyslipidemia is usually shows an increase in total triglyceride and a decrease of high-density lipoprotein (HDL)-cholesterol plasma concentrations and has been observed in schizophrenia patients.[7] Atypical antipsychotics, like, dibenzodiazepines and thienobenzodiazepines, are the mostly associated with the development of hyperlipidemia.[8] A study of examining gene expression in whole blood, fatty acid biosynthesis genes FASN (fatty acid synthase) and SCD (stearoyl-CoA desaturase) were over expressed in the patients with olanzapine compared with unmedicated patients. Moreover, subchronic administration of olanzapine also elevates serum triglycerides levels. Besides, the expression of lipogenic SREBP-1-controlled genes is unregulated.

However, haloperidol and several second generation antipsychotic drugs like clozapine, quetiapine, olanzapine, risperidone and ziprasidone were also found to have the ability to inhibit cholesterol biosynthesis by determining the incorporation of radioactive acetate into cholesterol. Kristiana et al.[9] In contrast, some found that clozapine, olanzapine and risperidone increase cholesterol biosynthesis in primary cultures of rat hepatocytes.

AIM AND OBJECTIVES

To assess the relation between lipid profiles (TC, TG, HDL, LDL) in the patients who are under the treatment of atypical antipsychotic drugs.

MATERIALS AND METHODS

A Prospective Observational Study (Follow-Up Study) was conducted patients from Psychiatric Department in a Tertiary Teaching Hospital RIMS, Kadapa and MNR Hospital, Hyderabad simulatenously.

Data Collection

- Patients visiting the psychiatric department are recruited for data collection in the study.
- Cases of mental illnesses, for example, schizophrenia, depression, psychosis, bipolar disorder, eating disorders, etc. can be found.
- Data collection took place during Jan 2015 to September 2015. Participants' demographics information such as age, gender, diagnosis, date of diagnosis, medication (most frequently used) and lipid profile were taken. For medication, most of the patients use the same antipsychotics during the treatment.
- For lipid level, triglyceride, Total Cholesterol, High-density lipoprotein (HDL) and Low-density lipoprotein (LDL) were tested.
- No intervention or treatment was conducted during the study.

Sample Size

- 46 subjects

Eligibility Criteria

There are obstacles when sampling. Inclusion and exclusion criteria were set for selecting participants before.

Inclusion Criteria

- Adult patients of ages 18 to 55 yrs.
- Patients undertaking treatment with antipsychotic drugs for first time.
- Patients with base-line values of lipid profile.
- Patients willing to participate in our study.

Exclusion Criteria

- Patient of ages below 18 years and above 55 years.
- Pregnant women are excluded from the study.
- Patients already under atypical antipsychotic treatment.
- Patients with co-morbid diseases like diabetes, hypertension and other cardiovascular diseases.
- Patients who are not willing to participate in the study.

Study Procedure

- Recruitment of patients based on the eligibility criteria.
- The risk factors and complications were assessed through the patient or care taker interview.
- Regular follow-ups of patients to monitor the therapy outcomes or signs, symptoms and progressions were done.
- Periodical measurements of lipid level every 8 weeks were done.
- The incidence rate was calculated.
- Data processing and analysis were done.
- Results were formed.

RESULTS

A prospective observational study was conducted in two South Indian Tertiary Care Teaching Hospitals simulatenously, RIMS, Kadapa and MNR hospital, Hyderabad for a period of 9 months. A total of 46 patients were recruited under inclusion criteria upon receival of ICF.

DISTRIBUTION BASED ON GENDER

Out of 46 patients being recruited 18 (39.13%) were female and 28 (60.86%) are male; results were shown in table and figure below.

TABLE: 4.1.

GENDER	NO. OF PATIENTS	PERCENTAGE
FEMALE	18	39.13%
MALE	28	60.86%

TABLE: 4.2.

NUMBER OF PATIENTS	PERCENTAGE
9	19.56%
19	41.30%
8	17.39%
7	15.21%
3	6.52%

TABLE: 4.3.

NAME OF THE DISEASE	NUMBER OF PATIENTS	PERCENTAGE
DEPRESSION with PSYCHOSIS	11	23.91%
SCHIZOPHRENIA	12	26.08%
BPAD - MANIA	7	15.21%
PSYCOSIS [NOD]	9	19.56%
MENTAL RETARDATION	7	15.21%

DISTRIBUTION BASED ON AGE

Out of 46 patients; 9 (19.56%) patients were found below the age of <20 years, 19 (41.30%) were found to be in between 20-30 years, 8 (17.39%) were found to be in between 30 – 40 years, 7 (15.21%) were found to be in between 40 – 50 years and 3 (6.52%) patients of age >50 years; and the results are shown in the table and figure.

DISTRIBUTION BASED ON DISEASE

Out of 46 patients being recruited, 11 (23.19%) were diagnosed as depression with psychosis, 12 (26.08%) with schizophrenia, 7 (15.21%) with mania, 9 (19.46%) with psychosis (NOD), 7 (15.21%) with mental retardation.

DISTRIBUTION BASED ON ATYPICAL ANTIPSYCHOTICS PRESCRIBED

Out of 46 patients, 11 (23.91%) patients are treated with Olanzapine (5mg), 12 (26.08%) patients are treated with Olanzapine (10mg), 7 (15.21%) patients are treated with Risperidone (2mg), 5 (10.86%) patients are treated with Risperidone (3mg), 7 (15.21%) patients are treated with the combination of Olanzapine + Clozapine, 4 (8.69%) patient is treated with the combination of Risperidone + Clozapine.

TABLE: 4.4.

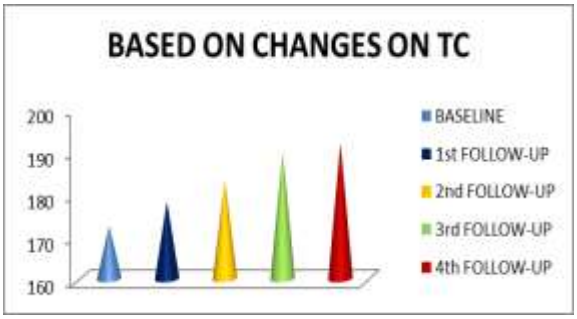
Name of the atypical antipsychotic	Dose of drug Prescribed (mg)	Number of patientsbeing prescribed	Percentage
OLANZAPINE	5	11	23.91%
OLANZAPINE	10	12	26.08%
RISPERIDONE	2	7	15.21%
RISPERIDONE	3	5	10.86%
OLANZAPINE + CLOZAPINE	10 + 50	7	15.2%
RISPERIDONE + CLOZAPINE	3 + 50	4	8.69%

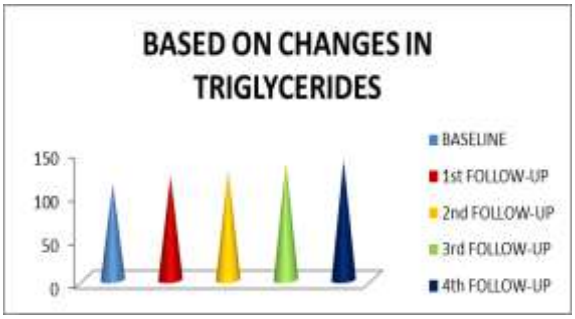
DISTRIBUTION BASED ON CHANGES IN LIPID ROFILE (TC, TG)

Average TC of patients at baseline = 172.43
Average TC of patients at 1st follow-up = 178.13
Average TC of patients at 2nd follow-up = 183.17
Average TC of patients at 3rd follow-up = 189.78
Average TC of patients at 4th follow-up = 191.86
Significant p value is < 0.0001.

DISTRIBUTION BASED ON CHANGES IN TRIGLYCERIDES

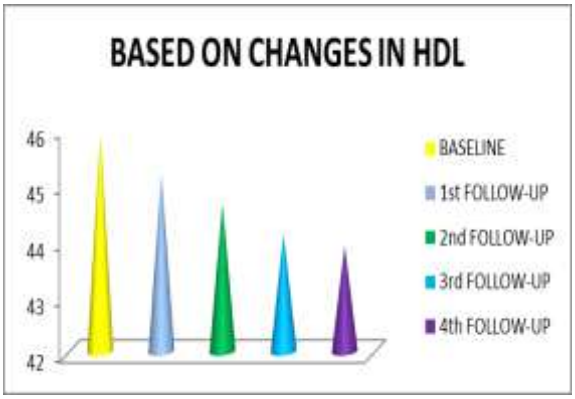
Average TG of patients at baseline = 110.25
Average TG of patients at 1st follow-up = 118.56
Average TG of patients at 2nd follow-up = 125.47
Average TG of patients at 3rd follow-up = 133.73
Average TG of patients at 4th follow-up = 36.90
Significant p value is < 0.0001.





DISTRIBUTION BASED ON CHANGES IN HDL

Average HDL of patients at baseline = 45.86
Average HDL of patients at 1st follow-up = 45.17
Average HDL of patients at 2nd follow-up = 44.65
Average HDL of patients at 3rd follow-up = 44.10
Average HDL of patients at 4th follow-up = 43.89
Significant p value is < 0.0001



DISTRIBUTION BASED ON CHANGES IN LDL

Average LDL of patients at baseline = 100.08
Average LDL of patients at 1st follow-up = 102.08
Average LDL of patients at 2nd follow-up = 103.30
Average LDL of patients at 3rd follow-up = 103.15
Average LDL of patients at 4th follow-up = 104.66
Significant p value is < 0.6609

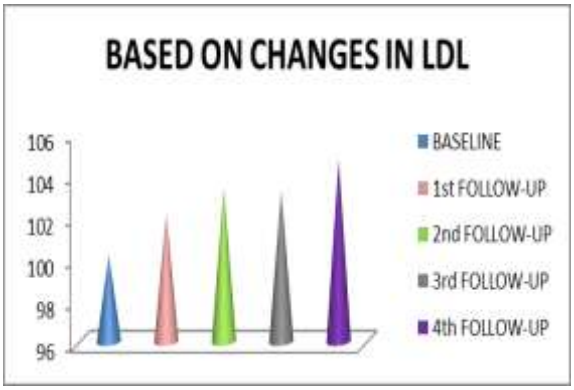


TABLE: 4.5: DISTRIBUTION BASED ON AVERAGE INCREASE IN LIPID LEVELS

Name of theAAPs	Percentage (no. of patients)	Change in TC mgs/dl)	Change in HDL (mgs/dl)	Change in LDL (mgs/dl)	% of CV of drugs
OLANZAPINE (5mg)	23.91%	14.5	-0.15	1.46	82.99
OLANZAPINE (10mg)	26.08%	22.03	-0.52	1.08	105.65
RISPERIDONE (2mg)	15.21%	11.75	-0.54	1.12	68.21
RISPERIDONE (3mg)	10.86%	9.67	-0.90	0.98	85.34
CLOZAPINE (10mg) + RISPERIDONE (3mg)	15.2%	28.0	-0.88	1.66	88.46
OLANZAPINE (10mg) + CLOZAPINE (50mg)	8.69%	13.25	-0.72	2.42	75.46
% of CV of metabolic disorders		33.02	6.89	15.44	

- Indicates decrease in magnitude.

TABLE: 4.6. Distribution Based On Percentage Increase Of Lipid Profile

LIPID PROFILE	ASCENDING ORDER OF DRUGS
TRIGLYCERIDES	OLANZAPINE > [OLANZAPINE + CLOZAPINE] > [CLOZAPINE + RISPERIDONE] > RISPERIDONE
TOTAL CHOLESTROL	[CLOZAPINE+ RISPERIDONE] >OLANZAPINE > [OLANZAPINE + CLOZAPINE] > RISPERIDONE
HDL	OLANZAPINE > RISPERIDONE > [CLOZAPINE + RISPERIDONE] > [OLANZAPINE + CLOZAPINE]
LDL	[OLANZAPINE + CLOZAPINE] > [CLOZAPINE + RISPERIDONE] > OLANZAPINE > RISPERIDONE

- Indicates decrease in magnitude.

DISCUSSION

Markers of lipid abnormalities and predictors of cardiovascular diseases are also always altered with psychiatric patients presenting with low HDL, high TG and elevated free fatty acids.

As the raised lipid levels are predictive of cardiovascular diseases, the long term health consequences for psychiatric patients are considerable.

Our original aim was to explore the atypical antipsychotics and lipid levels of patients in the psychiatric department of two different tertiary teaching hospitals simultaneously.

Invitro studies, animal models and studies conducted in children with first time use of atypical antipsychotics and evidence of comparable side effects in other psychiatric disorders provide support of atypical antipsychotics induced adverse effects. Our study was supported by Karen L. Teff," Atypical antipsychotics and the neural

regulation of food intake and peripheral metabolic disorder is more in psychiatric patients on atypical antipsychotic therapy.[10]

Out of 46 patients 9(19.56%) patients belongs to the age group of <20 years, 19(41.30%) patients belong to the age group of 20-30 years, 8(.45%) patients belongs to the age group of 30-40 years, 2(8.69%) patients belongs to the age group of 40-50 years. Our study was supported by Amareswara Reddy G et al, "A pilot study on the drug-drug interactions among the schizophrenia patients in a tertiary care teaching hospital" (2013).[11]

Out of 46 patients being recruited, 11 (23.19%) were diagnosed as depression with psychosis, 12 (26.08%) with schizophrenia, 7 (15.21%) with mania, 9 (19.46%) with psychosis (NOD), 7 (15.21%) with mental retardation.

Out of 46 patients, 11 (23.91%) patients are treated with Olanzapine (5mg), 12 (26.08%) patients are treated with Olanzapine (10mg), 7 (15.21%) patients are treated with Risperidone (2mg), 5 (10.86%) patients are treated with Risperidone (3mg), 7 (15.21%) patients are treated with the combination of Olanzapine + Clozapine, 4 (8.69%) patient is treated with the combination of Risperidone + Clozapine.

Of the 46 patients it was found that there is significant increase in total cholesterol and observed that there is an average increase in total cholesterol up to 28 mg/dl in patients receiving Combination of Risperidone + Clozapine and up to 22.03 mg/dl in patients receiving Olanzapine. Our study was supported by Mackin et al, "Metabolic disease and cardiovascular risk in people treated with antipsychotics in the community" (2007) assessed increase in fasting cholesterol.[12] In our study it showed the extreme significant value ($p = 0.0001$).

In our study we also observed that the level of triglyceride increased to an average of 31.2 mg/dl in patients taking olanzapine (10mg) and up to 28 mg/dl in patients receiving Olanzapine (5mg), up to 19 mg/dl in patients receiving combination of Olanzapine + Clozapine and 18 mg/dl in patients receiving Risperidone (3mg). Our study was supported by Sheitman et al, "Olanzapine induced elevation of plasma triglyceride levels" (1999) reported that the level of triglycerides increased from a mean of 170 mg/dl to 270 mg/dl in patients receiving Olanzapine.[13] The extreme significant value ($p = 0.0001$) was found.

Here in our study we did not find any significant changes in both HDL and LDL with the use of atypical antipsychotics might be due to the changes might be related to the changes in the diet and life style modifications of the patients. In our study it showed significant values (p) of 0.0010 and 0.6609 for HDL and LDL respectively. [NOTE: For the above calculation of significant value Graph Pad was used.].

Since Coefficient of Variation (CV) is of great practical significance and is the best measure of comparing the variability or consistency of two or more samples it is used as statistical method to compare the results. The percentage of CV also gives the same results comparatively.[14]

From statistical methods, percentage of CV was calculated for the drugs and the highest percentage of 105.65 was noted for the Olanzapine (10mg) and next the combination drugs Clozapine (10mg) + Risperidone (3mg) shown 88.46%; these results of percentage of CV shows that the drugs with highest value of percent of CV are more to show these variations in the lipid profiles of the patients.

The drugs tends to cause increased levels of lipid levels fall in the order, OLANZAPINE (10mg) > CLOZAPINE (10mg) + RISPERIDONE (3mg) > RISPERIDONE (3mg) > OLANZAPINE (5mg) > OLANZAPINE (10mg) + CLOZAPINE (50mg) > RISPERIDONE (2mg).

The tendency of drugs to cause each lipid levels fall in the order:

CONCLUSION

Atypical antipsychotics are producing an increased incidence of metabolic diseases. AAPS induced increased lipid levels is the most serious adverse effect, apart from hyperlipidemia there are other metabolic syndromes like lipid abnormalities, increase in blood glucose level which are predictors of cardiovascular disease. Moreover, the managing of psychiatric disorders should be multidisciplinary including cardiologist, psychiatrist and paramedical staff. Treatments should include medical (antihyperlipidimics, anti-psychotics) and psychotherapeutic interventions so that patients can have better services.

So while we institute antipsychotic therapy a careful monitoring of at-risk patients may aid in the prevention of metabolic syndrome as well as the management of any potential symptoms should they occur, suitable life style modifications are also obligatory. Finally this study requires further continuation of the research for better patient care.

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