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Metabolic effects of olanzapine therapy in schizophrenia patients

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Abstract
Background: The study is to access and compare the long term metabolic adverse effects of olanzapine monotherapy and combined therapy with other antipsychotic in schizophrenia patient on maintenance therapy, to identify the metabolic derangements in patients under monotherapy, combined therapy and other antipsychotic agents. The prospective observational study was conducted in Department of Psychiatric, Rajah Muthiah Medical College Hospital (RMMCH) over 100 patients. The patients/patient care givers were interviewed individually and the entire session was carried at optium privacy to create a favorable environment of acquiring data and providing education. The study shows that combined therapy was more preferred than monotherapy and typical antipsychotics in schizophrenia patients. In this study, WHO Quality of Life BREF, a general questionnaire was selected for evaluating outcome of treatment by measuring the quality of life mainly in four domains, these domains are physical health, psychological, social relationship and environmental domains. In this research the WHO quality of life will be metabolically effected more in monotherapy. This study accomplishes baseline data for future reference.

Keywords: monotherapy, combined therapy, olanzapine, quality of life (QOL)

Introduction
Schizophrenia is a disabling mental illness with a lifetime prevalence of 0.7% worldwide and significant, often devastating, consequences on social and occupational functioning. This disorder is slightly more common in men. Schizophrenia typically manifests in young people in their twenties, is usually lifelong and is characterized by 'positive symptoms' such as auditory hallucinations, bizarre delusions, and disrupted speech ('thought disorder') and by 'negative symptoms' such as social withdrawal, demotivation, self neglect, and the appearance of flat affect. Subtle cognitive impairment is also a feature.
The atypical property of Olanzapine is probably one of the main reasons for its clinical effectiveness in treating a heterogeneous disease like schizophrenia. Main goals of olanzapine include relapse prevention, recovery, improved an adherence to therapy and to improve quality of life. It displays high pharmacological profile with potent activity at dopamine, serotonin, muscarinic, histamine and adrenergic receptors. Drug-Induced weight gain, glucose dysregulation and elevated lipids are common side-effect of atypical antipsychotic drugs.
This study aim to assess and compare long term metabolic adverse effects of olanzapine monotherapy and combined therapy with other antipsychotic in schizophrenia patients on maintenance therapy. Periodic monitoring of BMI, glucose, lipids and QOL. Healthy lifestyle interventions are essential to counter adverse metabolic effects of olanzapine.

Materials and methods
The present study was designed as a prospective observational study. The study will be conducted in Department of Psychiatric, Rajah Muthiah Medical College Hospital, Annamalai University, Annamalai Nagar, Tamil Nadu, After receiving approval from the Hospital authorities and Institutional Human Ethics Committee. Which is a 1400 bedded multi-speciality tertiary care teaching hospital located in rural South India. The study period was 6 months i.e., from November 2016 to April 2017. The subjects selected are the patients who were referred to Department of Psychiatric at RMMCH. The study procedure was completely explained to the patients and a patient consent form was collected from them. Patients included in the study were selected in Schizophrenia patients on maintenance therapy, Patients of all age group, Patients of both the genders.
Data collection forms were formulated which procured information at baseline and each follow-up regarding patients adverse effects and duration of drug in take. The data required for our study was collected from the patients (if cooperative)/ care givers in inward and outpatient ward of Psychiatric Department in RMMCH. The various resources used for the collection of the data include Patient case sheet/patient medication record, Personal interaction with the patients. The patients/patient care givers were interviewed individually and the entire session was carried at optimum privacy to create a favourable environment of acquiring data and providing education. Each session lasted for a period of approximately 15 - 20 minutes.
Patients being recruited in our study were educated about their disease, ways to control the disease, and lifestyle modifications by the pharmacists under physicians guidance. This enabled to reinforce a positive attitude among the patients. Greater effort was taken to educate them about the need for adhering to the treatment regimen throughout their stay in hospital for patients coming under our study period.
The following demographic characteristics were obtained using a questionnaire: age and sex, duration of illness, details

of medication, and duration of medical treatment. The patients blood collection for lipid blood tests and measurement of blood glucose. BMI was calculated after measuring patients' weight and height (kg/m^2). Blood pressure was measured with an aneroid sphygmomanometer in an office setting. The content of WHO QOL BREF, a general questionnaire was selected for evaluating outcome of treatment by measuring the quality of life mainly in four domains; these domains are physical health, psychological, social relationship and environmental domains. Average daily dose was calculated based on the define daily dose calculation.

Statistical analyses

Simple descriptive statistics (means, standard deviations and 95% confidence interval) were generated for all continuous variables. For discrete variables number of patients and percentages are given. The difference between the two group means was analyzed by student's t-test. The difference between the two group proportions was analyzed by pearson's chi-squared test, and fisher's test where appropriate. The significance level was set at $p<0.05$. Multivariate logistic regression was used to access predictors of MetS. Analyses were performed using SPSS.

Results

Table 1: Duration vs RBS, T.CHOLESTEROL, BMI & QOL in olanzapine monotherapy

Duration	1	2	3	4	5	6	7	8	9	12	18	24
No of patients	2	3	7	4	4	4	2	2	1	3	1	2
Average RBS (mg/dl)	92.5	98.3	107.7	114	127.5	134.5	146.5	147.5	162	169	170	171.5
Average tot.cholesterol (mg/dl)	165	178.3	198.7	205.8	227.5	243.2	244	244	256	310.7	343	358
Average BMI	26.8	27.1	28.1	29.2	30.1	30.2	30.2	30.5	30.6	31.1	31.7	31.9
Average QOL	50	50	54	54	59	63	64	67	70	71	74	75

The table shows average RBS, T.CHOLESTEROL, BMI & QOL of the 35 patients under olanzapine monotherapy.

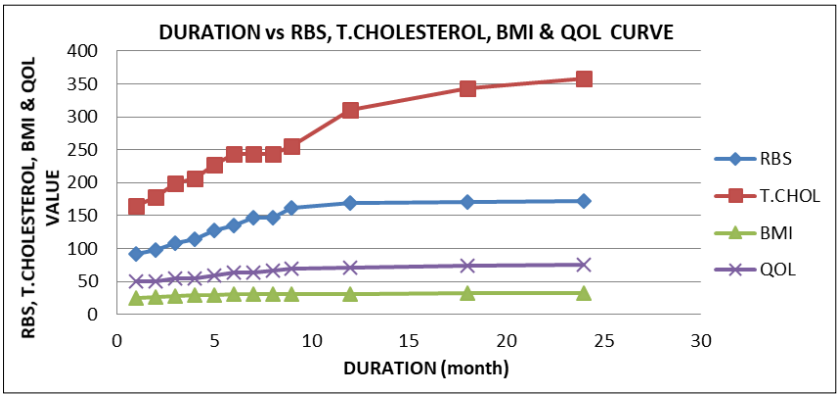

FIG 1: Duration VS RBS, T.CHOLESTEROL, BMI & QOL in Olanzapine Monotherapy

As the duration of treatment increased in patients on olanzapine monotherapy there was on increase in RBS, T.CHOLESTEROL, BMI & QOL.

Table 2: DURATION vs RBS, T.CHOLESTEROL, BMI & QOL IN OLAZAPINE COMBINE THERAPY

Duration	2	3	4	5	6	7	8	9	10	11	12
No of patients	2	1	5	5	5	1	4	3	1	1	2
Average Rbs (mg/dl)	85	95	103.4	116	125.2	129	133.8	134	134	136	139
Average Tot.cholesterol (mg/dl)	154	160	179.4	183.6	202	216	220	221	226	262	275
Average Bmi	18.2	19	21.5	22	23.5	24	24.6	24.7	24.8	25	25.4
Average Qol	45	46	49	52	52	53	57	57	57	57	61

The table shows average RBS, T.CHOLESTEROL, BMI & QOL of the 30 patients under olanzapine combined therapy.

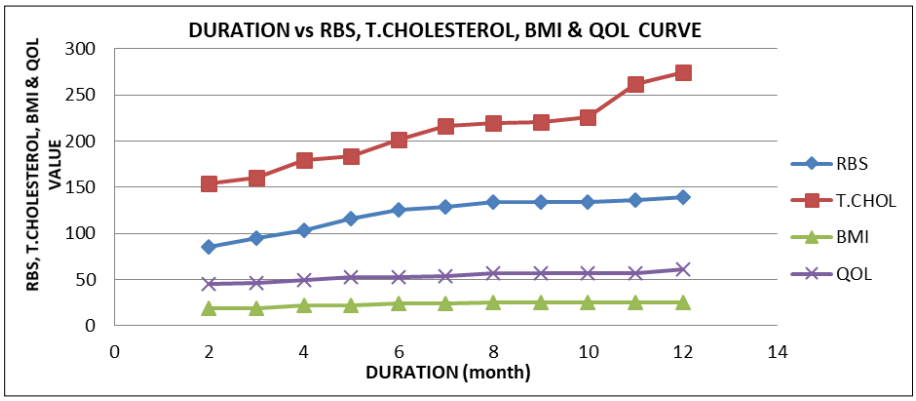

Fig 2: Duration vs RBS, T.CHOLESTEROL, BMI & QOL in olazapine combine therapy

As the duration of treatment increased in patients on olanzapine combined therapy there was on optimum increase in RBS, T.CHOLESTEROL, BMI & QOL but not accounting to the increase seen in olanzapine monotherapy.

Table 3: Duration vs RBS, T.CHOLESTEROL, BMI & QOL in typical antipsychotics

DURATION	4	5	6	7	8	9	10	11	12	13
NO OF PATIENTS	2	3	10	1	5	6	3	2	2	1
AVERAGE RBS (mg/dl)	77.5	85.3	86.1	100	83.6	90	90.3	88.5	91	100
AVERAGE TOT.CHOLESTEROL (mg/dl)	166.5	172.3	180.6	187	161.2	176.6	173.3	181	180.5	184
AVERAGE BMI	21.7	22.2	21.8	22.4	21	21.5	22.8	20.5	22	23.4
AVERAGE QOL	30	31	32	34	38	39	43	45	49	50

The table shows average RBS, T.CHOLESTEROL, BMI & QOL of the 35 patients under typical antipsychotic therapy.

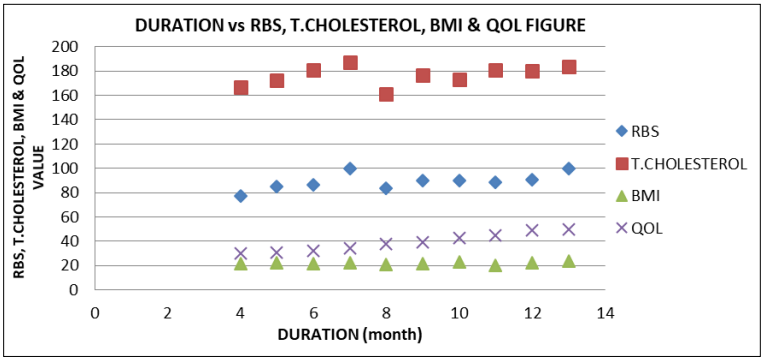

Fig 3: Duration vs RBS, T.CHOLESTEROL, BMI & QOL in typical antipsychotics

As the duration of treatment increased in patients on typical antipsychotics the average RBS, T.CHOLESTEROL, BMI showed no changes, but QOL was increased in patients on typical antipsychotics the rise was not as good as seen in olanzapine monotherapy & combined therapy.

Table 4: Relationship between olanzapine, olanzapine combination, typical antipsychotics treated patients and their collecting parameters value:

Therapy	Parameters		Mean	Std. deviation	F	*P* - value
Olanzapine (35 - patients)	Rbs	B	92.8286	16.68653	6.806	0.000
		A	128.80	26.44061		
	T.chol	B	168.03	38.07229	5.836	0.000
		A	233.89	54.84029		
	Bmi	B	21.7600	1.14100	20.705	0.000
		A	29.3143	1.83225		
Olanzapine combination (30 - patients)	Rbs	B	104.47	14.76186	3.601	0.001
		A	120.07	18.57684		
	T.chol	B	195.27	67.88120	0.437	0.664
		A	201.57	40.32513		
	Bmi	B	21.8967	2.13501	1.814	0.075
		A	22.9200	2.23320		

Typical antipsychotics (35 - patients)	Rbs	B	84.4571	9.26201	1.381	0.172
		A	87.4286	8.72551		
	T. chol	B	173.97	12.07692	0.465	0.644
		A	175.31	12.10924		
	Bmi	B	21.8714	1.08752	0.351	0.727
		A	21.7771	1.15837		

Table 5: Relationship of QOL

QOL	N	Mean	Std. Deviation	F	*p*- value
Olanzapine	35	59.9143	8.16150	73.555	0.000
O+C Drugs	30	52.9000	7.47109		
Typical anti psych drugs	35	37.2857	8.19100		
Total	100	49.8900	12.51818		

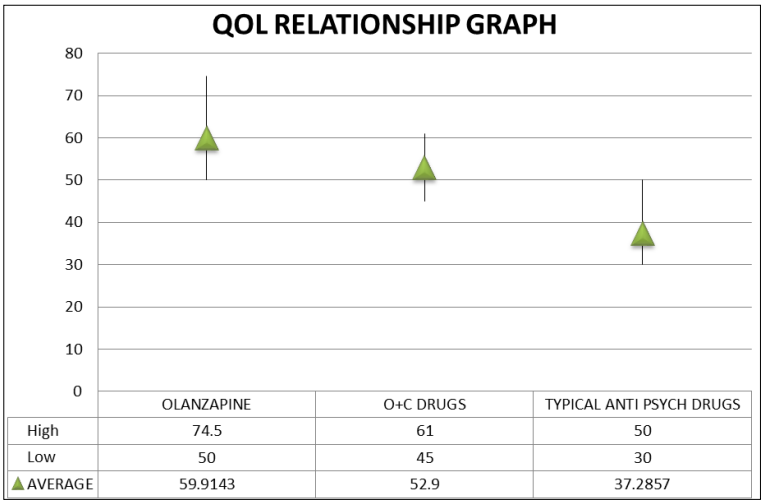

Fig 4: Relationship between QOL & olanzapine monotherapy, combine therapy, typical antipsychotic therapy.

The figure depicts that QOL was better in patients on olanzapine monotherapy & combined therapy, then those on typical antipsychotics alone.

Table 6: Chlorpromazine Equalent

CPMZ	N	Mean	Std. Deviation	F	*p*- value
OLANZAPINE	35	389.29	108.34411	1.879	0.158
O+C DRUGS	30	422.50	95.44587		
TYPICAL ANTI PSYCH DRUGS	35	372.86	106.99289		
Total	100	393.50	105.08654		

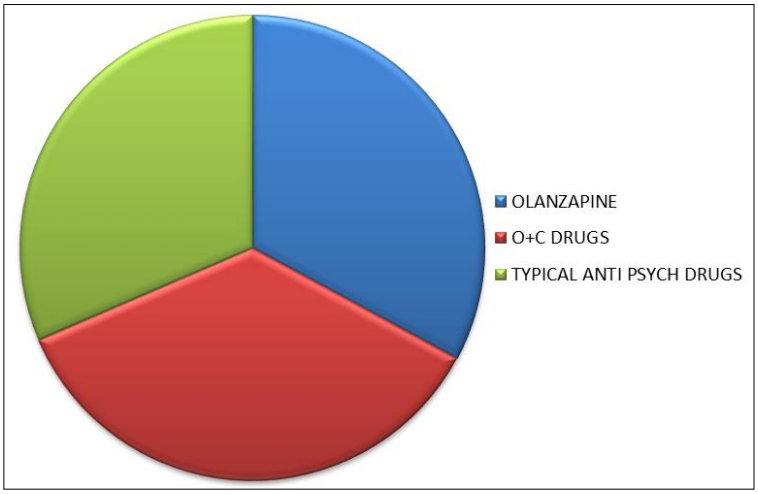

Fig 5: Chlorpromazine equalent of olanzapine monotherapy, combine therapy, typical antipsychotic therapy.

The dosage of antipsychotics in the each of the 3 groups are not significantly different.

Table 7: Relationship of data's

Average	RBS	T.CHOL	BMI	QOL
Olanzapine	128.80	233.89	29.3143	59.9143
O+C Drugs	120.07	201.57	22.9200	52.9000
Typical Anti Psych Drugs	87.4286	175.31	21.7771	37.2857

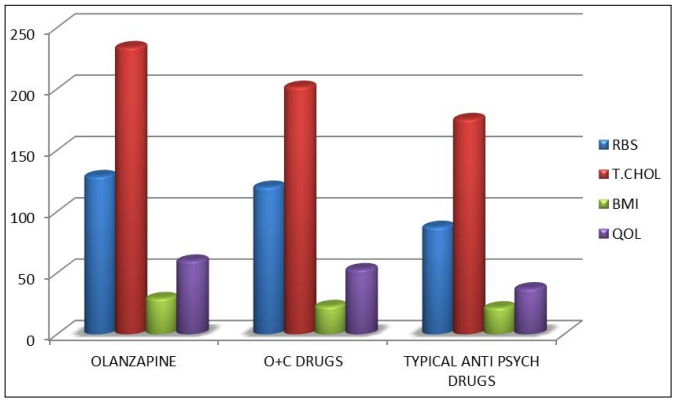

Fig 6: Graph Comparing all the Results

Define daily dose

The DDD is the assumed average daily maintenance dose for the medication's main indication. It is defined globally for each medicine by the WHO Collaborating Centre for Drug Statistics.

The units in the recommended dose of a medicine may be milligrams for solid oral formulations like tables and capsules or millilitres for liquid oral or injection formulations. Converting aggregate quantities available from pharmacy inventory records or sales statistics into DDDs roughly indicates how many potential treatment days of a medicine have been procured, distributed or consumed. The medicines can then be compared, using units such as:

- No. of DDD per 100 beds per day (100 bed-day), for hospital use.

DDD GIVEN FOR 100 BED-DAYS:

$$\text{DDD of RMMCH (for 100 bed-days)} = \frac{100 \times \text{units} \times \text{strength}}{\text{DDD} \times \text{period of study} \times \text{bed strength} \times \text{occupancy}}$$

$$\text{Where, occupancy index} = \frac{\text{Total inpatient} - \text{days} \times 100}{\text{Available beds} \times \text{study period}}$$

Table 8

Drug name	ATC Code	DDD (WHO)	Number of DDD
Olanzapine	N05AH03	0.01g	3.5
Haloperidol	N05AD01	0.008g	12.5
Chlorpromazine	N05AA01	0.3g	2.8

Discussion

CATIE: Liberman JA, *et al* (2005) among patients with schizophrenia, patients receiving olanzapine experienced a longer time to discontinuation compared with the other antipsychotic medications, but they experienced greater weight gain, hyperglycemia and hyperlipidemia.

In our study we compared olanzapine with haloperidol & chlorpromazine. We found olanzapine having higher metabolic syndrome. Which is similar to catie but unlike catie we did not shows discontinued rate. We also did not compare olanzapine with other atypical antipsychotics.

Musab M. Khalaf *et al* (2013) study demonstrated that olanzapine and risperidone treatment for 8 weeks caused significant increase in BMI, serum leptin levels and also causes deleterious effects on lipid profile. There were also no significant differences between olanzapine and risperidone with regard to their effects on leptin, cholesterol, HDL, LDL and atherogenic index.

According to our study treatment with olanzapine monotherapy showed significant increase in BMI, Total cholesterol level but when olanzapine was combined with typical antipsychotics the increase in BMI, Total cholesterol was optimum.

Cătălina Crian *et al* (2004) observed in their study the rate of obesity and metabolic disorders were higher in pat ients treated with second generation antipsychotics.

Similarly in our study the rate of obesity indicated by BMI & metabolic disorders indicated by RBS & Total cholesterol were higher in patients treated with olanzapine monotherapy & combined therapy than first generation antipsychotics.

Ankesh Barnwal *et al* (2012) showed that all antipsychotics can cause significant abnormalities in carbohydrate and lipid metabolism. Selection of antipsychotics, particularly the newer ones requires consideration of co morbidities like obesity, diabetes mellitus and dyslipidemias. During antipsychotic drug therapy periodic monitoring for metabolic abnormalities is advisable.

Accordingly in our study patients treated with olanzapine (newer antipsychotics) required consideration in patients comarbilities like obesity, diabetes, dyslipidemia & hence requires periodic monitoring for metabolic abnormalities.

Dr. R Venkata Ramudu *et al* (2015) this study shows that SGAs cause metabolic disorders in the particular order olanzapine (10mg) > clozapine (10mg) + risperidone (3mg) > risperidone (3mg) > olanzapine (5mg) > olanzapine (10mg) + clozapine (50mg) > risperidone (2mg).

In concordance with our study olanzapine has an increase incidence on metabolic diseases also (blood glucose, total cholesterol, weight gain). This shows the management of psychiatric disorders should be be multidisciplinary including psychiatrist, diabetologist and paramedical staff.

Irena Popović *et al* (2015) this study showed that high rate of MetS in patients treatment with olanzapine which exceeds MetS prevalence in general population. Hence regular monitoring of cardio metabolic risk factor was highly recommended. The need for some other drug other than olanzapine the long term treatment of schizophrenia was also indicated.

This was supported in our study as long term schizophrenia were maintained either on low dose olanzapine monotherapy or combined with typical antipsychotics in order to reduce the metabolic side effects.

Conclusion

Combined therapy has the benefit of both typical and atypical drugs. It is possible that both of them when administered at lower range of dosages minimised the side effect profile. When the drugs are given in monotherapy their side effect profiles namely the metabolic effects with olanzapine and extra pyramidal effects with typical first generation dugs reduce quality of life. Combined therapy more preferable to monotherapy.

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