Available Online at www.ijpba.in

ISSN: 2349 - 2678

International Journal of Pharmaceutical and Biological Science Archive 2 (6) 2014, 07-13

RESEARCH ARTICLE

Metabolic derangements among the Schizophrenia patients consuming second generation atypical antipsychotics-Olanzapine and Aripiprazole: a randomised controlled trial.

Debkumar Ghosh[1], Dibakar Haldar [2], Abhik Sinha [3], Dhruba Mandal [4], Mohana Sinha[5], Palash Das[6]

[1] Medical Teacher on Trainee Reserve, Department of Biochemistry, Bankura Sammilani Medical College, Bankura, West Bengal, India.
[2] Associate Professor, Department of Community Medicine, R. G. Kar Medical College, Kolkata. India.
[3] Assistant Professor, Department of Community Medicine, R. G. Kar Medical College, Kolkata, India.
[4] Associate Professor, Department of Anatomy, Bankura Sammilani Medical College, Bankura, India.
[5] Senior Resident, Ophthalmology, Calcutta National Medical College, Kolkata, India.
[6] Associate Professor, Community Medicine, College of Medicine & Sagar Dutta Hospital, India.

ABSTRACT

Background-Inspite of their superiority over first generation antipsychotics to improve the quality of patients' life by controling both positive as well as negative symptoms SGAs are critisised for extra risk of cardiovascular diseases by dint of their metabolic derangements. **Objectives**: to compare the metabolic derangement resulting from Aripiprazole and olanzapine therapy. **Methodology**- an open label randomized controlled trial was carried out for one year among schizophrenia patients attending psychiatry OPD of R G Kar Medical College. After obtaining consent equal number of male and female diagnosed schizophrenia patients were allocated into two study arms i.e. aripiprazole and olanzapine groups by "randomization by minimization". Baseline information was assembled by interview, clinical examination and record review using a predesigned questionnaire followed by laboratory investigation at Biochemistry department. Same set of information was collected in similar fashion during follow up visits scheduled at 6 weeks and 12 weeks. **Results**: at 12 weeks the aripiprazole group showed increase only in BMI and TC among 7.5% and 22.5% of patients with average weight loss by 1.78±0.83 kg (mean±sd). Olanzapine group showed average increase in Weight: 8.91±3.4 kg, BMI: 4.53±1.74 kg/m^2, FPG: 33.63±13.83, TC: 18.03±39.49, TG: 23.68±21.08, HDL: -6.51±6.22, LDL: 30.42±31.64. The hike in MeS was from 7.5% to 7.5% i.e. nil in gr.1 compared to 12.5% to 57.5% in olanzapine group. **Conclusion**: regarding metabolic effects Olanzapine came out to be inferior to aripiprazole. So prescribing of it demands physicians' skill for judicial patient's selection, dose determination and purposeful follow up investigations to detect early change for necessary therapeutic measures.

Key-words: atypical anti-psychotics, metabolic derangement, metabolic syndrome

INTRODUCTION:

Currently atypical second generation antipsychotics (SGA) are the most frequently prescribed drugs for schizophrenia.[1] They act by dual serotonin and dopamine antagonism.[2] Cumulating evidence indicates that these agents provide good antipsychotic effects with a lower risk of extrapyramidal symptoms (EPS) than typical antipsychotics.[3] They enhance patient's quality of life[4] with fewer relapses and reduced hospital stay, number of physician visits and overall care costs.[5] Although the use of atypical antipsychotics offers many benefits to schizophrenics, these drugs appear to be associated with weight gain along with varying degrees of metabolic adverse effects, such as impaired glucose metabolism, dyslipidemia and in some cases, more serious morbidity, such as cardiovascular disease.[6, 7] Epidemiological studies involving schizophrenia patients have documented a higher incidence of cardiovascular disease than in the general population, and patients with schizophrenia may be at an elevated risk for cardiovascular disease even in the absence of antipsychotic treatment. [8, 9, 10] This is likely due to higher rates of unhealthy lifestyle, obesity, lipid abnormalities, diabetes, hypertension, physical inactivity, poor compliance and smoking in this population.[8, 11, 12] It is more pertinent in Indian perspective as Indians in particular are more prone to develop metabolic side effects such as diabetes mellitus, dyslipidaemias and cardiovascular disease.[13] Asian Indians have a high prevalence of insulin resistance syndrome that may underlie their greater-than-normal tendency to develop

*Corresponding author: Dr. Dibakar Haldar |Email: dibahaldar@gmail.com

diabetes mellitus and early atherosclerosis. Important reasons could be their excess body fat and adverse body fat patterning, including abdominal obesity, even when the body mass index is within the currently defined limits.[13]

Consequently, it is important that health care professionals work together to monitor the metabolic functioning of patients with schizophrenia, who are at high risk for metabolic disorders.[14] Health care professionals also need to be aware of the potential metabolic impact of current pharmacologic treatments for schizophrenia.

Aripiprazole is a new addition to the atypical antipsychotic family. It is reported to work against negative symptoms of schizophrenia where other drugs have failed and has recently been approved for marketing in India. Therefore, a head-to-head comparison between aripiprazole and the established antipsychotic olanzapine was deemed worthwhile in the Indian context.

The evidence so far suggests that in terms of efficacy for schizophrenia, aripiprazole is superior to placebo and haloperidol (long term), similar to perphenazine and risperidone, and inferior to olanzapine. Its tolerability profile in patients with schizophrenia appears superior to haloperidol, perphenazine, risperidone, and olanzapine.[15]

R. G. Kar Medical College is a tertiary care teaching institution in Kolkata catering a huge number (daily at least 10 new patients) of patients suffering from major Psychosis. Paucity of study revealing the metabolic effects of these two SGAs in this region indulged the investigators to contemplate the present study with the objective to study the metabolic side effects among the patients taking SGA namely Olanzapine and Aripiprazole with special reference to the body mass index, waist-hip-ratio, FPG and Lipid Profile.

Methodology: An open label randomized controlled trial among the Schizophrenia patients was conducted for a period of one year in the out-patient-department (OPD) of Psychiatry medicine and Biochemistry department of R. G. Kar Medical College, a tertiary care teaching institution in Kolkata.

As per the literature, increase in weight more than 7% of the baseline was found 55% and 29% of study subjects on Olanzapine and Aripiprazole, respectively.[15] Considering these as the prevalence, the sample size for the present study was calculated based on the formula: N (for each arm)=$[(Z_\alpha + Z_\beta)^2\{(p_1q_1)+(p_2q_2)\}]/(p_1-p_2)^2$, where Z_α=1.65 (one way, as all studies confirmed that weight gain is more among Olanzapine consumers), Z_β=0.84 with 80% power of test, p_1=55, q_1=100-55; p_2=29, q_2=100-29. Accounting 10% drop out the sample size would be 40 in each arm of the study.

Inclusion criteria: 1. Male or female with age between 18-55 years, 2. Clinical diagnosis of schizophrenia with DSM IV-TR criteria, 3. Non-diabetic, Non-hypertensive and having no other medical illness, 4. Ready to attend for stringent regular follow up.

Exclusion criteria*:* 1. Pregnant or breast feeding women or planning a pregnancy, 2. Patient having hypersensitivity or allergy to the drugs under investigation, 3. Acute psychosis, acute suicidal ideation, or any other psychiatric condition that might require emergency intervention, 4. Any clinical condition or significant concurrent disease judged by the investigator to complicate the evaluation, 5. Having participated in other drugs investigation study and taken the drugs under this investigation within one month prior to the entry in the study.

Allocation of subjects: Equal number of diagnosed male and female schizophrenia patients fulfilling the inclusion-exclusion criteria was randomly allocated into two study arms by the process of 'ranomization by minimization'.

Information pertaining to demographics, clinical diagnosis, anthropometry, blood parameters was gathered by interview, clinical examination including anthropometry, scrutiny of records and laboratory examination.

Predesigned case record form, Weighing-machine, measuring tape, stethoscope, sphygmomanometer, respective reagent- kits for laboratory evaluation, Semi-auto analyzer and ELISA reader with washer etc. were used as tools for the present study.

After obtaining approval from the 'University of Health Science', West Bengal; Ethical clearance from 'Ethical Committee' of R. G. Kar Medical College, Kolkata data were collected with prior informed consent from the eligible patients/guardian. For each selected patient, 1st visit and 2nd Visit were scheduled for baseline data collection including laboratory investigations and follow up visits were paid to each participants at 6 weeks (3rd visit) and end of study (EOS) at 12 weeks (4th visit).

At the start base line information pertaining to demographics, clinical diagnosis etc. was collected in the Psychiatry department by interview and clinical examination including anthropometry.Then the patients was referred to the Department of Biochemistry for getting registered for laboratory investigations like Fasting plasma sugar (FPG), serum total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL) after 8 hours of fasting. In the next visit in the Biochemistry department, venous blood was collected from median antecubital vein of all study subjects. Blood samples were centrifuged and separated serum was used

for above mentioned biochemical tests. The 3rd and 4th visits were scheduled at 6 and 12 weeks after the inception of the study and same sort of clinical examination with anthropometry and laboratory investigations were done on each subject.

Data were compiled and analysed using table, calculating proportion/ percentage and applying inferential statistical tests like χ^2, Fisher exact & unpaired't' tests, relative risk (RR) with its 95% confidence interval (CI) etc. P value of ≤0.05 was considered as statistically significant. For data analysis SPSS 16 version was utilised.

RESULTS AND ANALYSIS:

Total 80 subjects were included in the study, 40 in each arm i.e. in Olanzapine and in Aripiprazole group. Out of 40, 26 i.e. 65.0 percent were female in each arm. Overall, average age was 29.46±8.34, with a median of 28.5 and range of 18 to 47 years. Female was found to have significantly lower age (t=2.022 at df=78, p=0.047).

However, the baseline between group variations in different attributes was kept in-significant via the process of 'randomization by minimization'. (Table-1)

After 12 weeks of therapy the picture became different. The Olanzapine group showed the values of all parameters higher than that of their counterpart and the differences were statistically robust enough to draw conclusion that this SGA has played a definite role to cause these metabolic derangements. (Table-2).

For exploring the within group metabolic alteration paired 't' was performed. In Aripiprazole group the increase was found in BMI, TC among 7.5%, 22.5% of patients, and 5.0% for each of TG, LDL and VLDL level. Mild weight gain was seen in 12.5% but weight loss was seen among the rest. And increase in HDL was universal. Considering the group average the weight loss was 1.78±0.83 kg and increase was observed only in BMI and HDL with 0.47±0.36 kg/m^2 (mean±sd) and 2.98±1.99 mg % hike from the baselvel.

In contrast the patients belonged to the Olanzapine group showed average increase in all the parameters except HDL. Individually, the increase was universal in weight, BMI, WHR, FPG, TG and VLDL. It was revealed that among 75.0%, 7.5%, and 97.5% of study subjects there was increase in TC, HDL and LDL, respectively. The average increases (mean±sd) were: Weight 8.91±3.4 kg, BMI 4.53±1.74 kg/m^2, WHR 0.091±0.047; FPG 33.63±13.83, TC 18.03±39.49, TG 23.68±21.08, HDL -6.51±6.22, LDL 30.42±31.64 and VLDL 4.74±4.22 mg%.

Analysis considering the patient-wise metabolic derangement it was revealed that at baselvel 20.0 & 17.5%, 12.5 & 32.5%, 45.0 & 52.5%, 15.0 & 17.5%, 10.0 & 27.5%, 12.5 & 7.5% of individuals belonged to gr.2 and gr.1 were found to have fulfill the criteria/values more or less than the recommended cut-offs for WC (≥80 cm for female and ≥90 cm for male), FPG(≥100 mg%), HDL (<40 mg% for male and <50 mg% for female), TG (≥150 mg%), Blood Pressure(≥130 SBP/85 DBP), metabolic syndrome (MeS) (as per the criteria set by international diabetes federation [IDF]). All the above cut-offs are set by the IDF. [16] High (for Asian Indians) BMI was found 15.0 & 30.0% of participants in gr.2 & gr.1. Moreover, 35.0 & 17.7% of the study subjects of respective groups had LDL cholesterol values higher than the cut-off (≥100 mg %) arbitrarily set up for the present study. Between group difference in proportion was only observed in BP without any variation across the gender. (Table-3)

At EOS significant between group variations in respect of criteria/values higher or lower than the recommended values were revealed in WC (62.5% in gr.2 Vs 17.5% in gr.1), FPG (90.0% Vs 5.0%), HDL (85.0% Vs 40.0%),TG (42.5% Vs 7.5%), BP (22.5% Vs nil), MeS (57.5% Vs 7.5%), BMI (100% Vs 30.0%) and LDL (87.5% Vs 12.5%). (Table-4)

Ananlysis revealed that overweight/obesity was present among 30% in gr.1 in both at baselevel and EOS whereas the corresponding figures for gr.2 were found to be 15% and 100%. Similarly the proportion of patients in gr.1 having metabolic syndrome (MeS) as per the criteria set by IDF at base level and at EOS were 7.5% each in contrast to the figures of gr.2 12.5% and 57.5%, respectively.

Table 1: Distribution of study subjects as per various baseline characteristics (N=80)

Parameter		*Olanzapine (mean±sd)*	*Aripiprazole (mean±sd)*	*Unpaired 't' at df 78*	*P value*
Demography	Age (yr)	28.07±7.08	30.85±9.42	1.489	0.140
Anthropometry	BMI	22.71±3.87	21.79±1.34	1.416	0.161
	WHR	0.89±0.053	0.85±0.04	0.146	0.884
Metabolic parameters	FPG	86.82±9.16	91.95±16.58	1.715	0.090
	TC	159.59±21.14	163.75±22.82	0.845	0.401
	TG	128.12±22.59	125.48±29.78	0.448	0.655
	HDL	46.68±5.83	44.86±8.94	1.076	0.285
	LDL	86.68±18.54	91.66±22.19	1.088	0.280

Table 2: Distribution of participants as per various characteristics after 12 weeks of treatment (N=80).

Parameter		*Olanzapine (mean±sd)*	*Aripiprazole (mean±sd)*	*Unpaired 't' at df 78*	*P value*
Anthropometry	BMI	26.34±1.63	23.17±3.97	4.661	0.000
	WHR	0.93±0.07	0.85±0.03	6.558	0.000
Metabolic parameters	FPG	120.45±15.41	78.17±7.80	15.481	0.000
	TC	186.82±31.54	148.61±23.43	6.151	0.000
	TG	151.80±28.20	111.35±25.14	6.771	0.000
	HDL	40.17±4.36	47.84±8.20	5.225	0.000
	LDL	124.45±30.65	78.51±17.95	8.19	0.000
	VLDL	30.36±5.64	22.27±5.03	6.769	0.000

Table 3: Distribution patients and different metabolic derangements as per base values (N=80)

Parameters		Base value, gr.2 [n_2=40], No. (%)	Base value, gr.1 [n_1=40], No. (%)	χ^2 at df 1,p	R R(95% CI)
WC	Male[n_1=14] (≥80cm)	-	-	NA	NA
	Female[n_2=26](≥90 cm)	8(30.77)	7(26.92)	-	-
	Total [n=40]	8(20.00)	7(17.5)	0.08,0.77	1.14(0.46-2.85)
FPG (≥100mg %)	Male	2(14.29)	6(42.86)	2.80,0.09	0.33(.08-1.38)
	Female	3(11.54)	7(26.92)	1.98,0.15	0.43(0.12-1.48)
	Total	5(12.5)	13(32.5)	4.59, 0.03	0.38(0.15-0.98)
HDL	Male (<40 mg %)	1(7.14)	3(21.43)	1.0*	0.62(0.07-5.41)
	Female (<50 mg %)	17(65.38)	18(69.23)	0.09,0.76	0.94(0.65-1.38)
	Total	18(45.00)	21(52.5)	2.46, 0.11	0.69(0.43-1.10)
TG (≥150mg %)	Male	3(21.43)	5(35.71)	0.677*	0.60(0.18-2.04)
	Female	3(11.54)	2(7.69)	1.0*	1.50(0.27-8.25)
	Total	6(15.00)	7(17.5)	0.09, 0.76	0.86(0.32-2.33)
BP(≥130/ 85mmof Hg)	Male	2(14.29)	4(28.57)	0.85,0.35	0.50(0.11-2.30)
	Female	2(7.69)	7(26.92)	3.36,0.06	0.29(0.07-1.25)
	Total	4(10.0)	11(27.5)	4.02, 0.04	0.36(0.13-1.05)
MeS	Male	-	-	NA	NA
	Female	5 (19.23)	3(11.54)	NA	NA
	Total	5(12.5)	3(7.5)	0.56,0.45	1.67(0.43-6.51)
BMI (≥23 kg /m^2)	Male	3(21.43)	11(78.57)	9.14,0.00	0.27(0.10-0.77)
	Female	3(11.54)	1(3.85)	0.61*	3.0(0.33-26.99)
	Total	6(15.0)	12(30.0)	2.58,0.10	0.50(0.21-1.20)
LDL (≥100mg %)	Male	7(50.0)	1(7.14)	0.03*	6.0(0.86-42.10)
	Female	7(26.92)	6(23.07)	0.10,0.75	1.17(0.45-3.00)
	Total	14(35.0)	7(17.5)	3.16,0.07	2.00(0.90-4.43)

*Fisher exact test

Table 4: Distribution patients as per different metabolic derangements at the end of study (N=80)

Parameters		Final value, gr.2 [n_2=40] , No. (%)	Final value, gr.1 [n_1=40], No. (%)	χ^2 at df 1,p	RR (95% CI)
WC	Male[n_1=14] (≥80cm)	7(50.0)	-	NA	NA
	Female[n_2=26](≥90 cm)	18(69.23)	7(26.92)	7.04,0.007	2.57(1.21-5.47)
	Total[n=40]	25(62.5)	7(17.5)	16.88,0.000	3.57(1.75-7.30)
FPG (≥100mg %)	Male	12(85.71)	-	NA	NA
	Female	24(92.31)	2(7.69)	33.92,0.000	12.0(3.13-45.65)
	Total	36(90.0)	2(5.00)	57.94,0.000	18.0(4.64-69.77)
HDL	Male (<40 mg %)	8(57.14)	1(7.14)	0.012*	8.00(1.15-55.80)
	Female (<50 mg %)	26(100.0)	15(57.69)	11.53,0.000	1.73(1.25-2.41)
	Total	34(85.0)	16(40.0)	17.28,0.000	2.13(1.42-3.17)
TG (≥150mg %)	Male	5(35.71)	1(7.14)	0.164*	5.00(0.67-37.51)
	Female	12(46.15)	2(7.69)	7.92,0.004	6.00(1.49-24.20)
	Total	17(42.5)	3(7.5)	13.07,0.000	5.67(1.80-17.83)
BP(≥130/85 mm of Hg)	Male	4(28.57)	-	NA	NA
	Female	5(19.23)	-	NA	NA
	Total	9(22.5)	-	NA	NA
MeS	Male	5 (35.71)	-	NA	NA
	Female	18(69.23)	3(11.54)	15.66,0.000	6.00(2.01-17.93)
	Total	23(57.5)	3(7.5)	22.79,0.000	7.67(2.50-23.51)
BMI(≥23)	Male	14(100)	11(78.57)	0.222*	1.27(0.97-1.67)
	Female	26(100)	1(3.85)	44.37,0.000	26.0(3.8-177.69)
	Total	40(100.0)	12(30.0)	43.08,0.000	3.33(2.08-5.35)
LDL (≥100mg %)	Male	12(85.71)	-	NA	NA
	Female	23(88.46)	5(19.23)	22.36,0.000	4.60 (2.07-10.24)
	Total	35(87.5)	5(12.5)	45.00,0.000	7.00(3.06-16.03)
TC (≥200 mg %)	Male	-	-	NA	NA
	Female	-	2 (7.69)	NA	NA
	Total	-	2 (5.00)	NA	NA

*Fisher exact test

DISCUSSION:

Psychosis is one of the most severe psychiatric disorders. It is characterised marked impairment of behavior serious inability to think coherently, lack of insight and inability to communicate properly. There are two types: acute psychotic episodes which tend to be self limiting and chronic psychosis which is difficult to treat and accounts for majority of antipsychotic drug use for continued life-long treatment.[17]

Conventional (typical, classical) antipsychotic agents antagonise the activity D_2 receptor in the hyperactive mesolimbic dopamine pathway in schizophrenic brain. These agents reduce positive symptoms like delusions and hallucinations. But they have substantial risk of extrapyramidal syndrome (EPS) and endocrine effects like increase in prolactin levels ultimately resulting into high rate of relapse.[18]

In addition, they can't reduce effectively the negative symptoms like emotional withdrawal and poor social functioning and may lead to further deterioration.

Novel (atypical, second generation) antipsychotics are as efficacious in treating positive symptoms as older agents coupled with better tackling of negative symptoms.[19] They are also associated with lower risk of EPS.

Currently, the newer atypical antipsychotic drugs are increasingly preferred over older typical antipsychotic medication due to their favorable adverse drug reaction profile.[20]

Aripiprazole is a new addition to the atypical antipsychotic family. It is reported to work against negative symptoms of schizophrenia where other drugs have failed and has recently been approved for marketing in India. Therefore, a head-to-head comparison between aripiprazole and the established antipsychotic olanzapine was deemed worthwhile in the Indian context.

In the present study, it was clearly revealed that the weight gain was universal and very high in Olanzapine group with an average of 8.91±3.4 kg compared to an average 1.78±0.83 kg weight loss in the counter group. In a review, Citrome L also reported mean weight change in Aripiprazole group -1.43 kg and in Olanzapine group +5.55 kg over a duration of 52 weeks.[15] In a double blind study Stock E et al observed that by week 26, 37% of olanzapine-treated patients had experienced significant weight gain compared with 14% of aripiprazole-treated patients. Statistically significant differences in mean weight change were observed between treatments beginning at Week 1 and sustained throughout the study. Changes in fasting plasma levels of TC, HDL, and TG were significantly different in the two treatment groups, with worsening of the lipid profile among patients treated with olanzapine.[21] In a double blind placebo controlled study Pual E K J et al also reported a slight decrease in mean body weight in aripiprazole group from baseline to endpoint (placebo: –0.8 kg; aripiprazole: –0.3 kg). No statistically significant difference in clinically significant weight gain (≥7% increase from baseline) was detected between the two groups (aripiprazole, N=2; placebo, N=0).[22] Form their observation Hamp D et al suggested that olanzapine is associated with greatest weight gain.[23] In this study it was found that the rise in FPG was universal phenomena in Olanzapine group with an average hike of 33.63±13.83 mg/dl over and above the base level value. In a retrospective study, Wirshing DA et al comparing glucose levels at baseline and during 2.5 years medication observed that mean glucose levels were significantly increased from baseline for patients treated with clozapine or olanzapine.[24] As per the present analysis olanzapine group showed a substantial increase in almost all plasma lipid fractions except HDL. This finding was in accordance with that of Lizheng S and Ritter LM.[25, 26] In the present study the proportion of patients found to have MeS at base level was 7.5% and 12.5% in gr.1 and gr.2, respectively. In their recent prospective study done in India in previously drug-naive patients with schizophrenia, Sahoo S et al reported an increased incidence of metabolic syndrome in 31.81 per cent cases after 6 weeks of therapy with a single antipsychotic drug in comparison to an incidence of 3.33 per cent at baseline.[27] Gautam S and his associates in their prospective study reported that 23.3% patients belonging to the olanzapine group developed metabolic syndrome.[28]

The relationship of SGAs to the development of major cardiovascular risk factors is of great interest, and led to a joint conference in November 2003 of the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity. The result was a consensus statement regarding antipsychotic drugs and diabetes.[7]

None of the treatment emergent adverse events were severe enough to warrant withdrawal of the study medication neither was any serious adverse event encountered which required hospitalizations. Study subjects showed excellent compliance.

Conclusion: The present study findings reinforce all the previous observation that all SAGs tend to cause abnormalities in carbohydrate and lipid metabolism leading to development of MeS and make the patients more vulnerable to cardiovascular diseases potentiating the risk imposed on them by the disease itself. The SAGs are like a sharp knife injudicious careless use of which may harm also the users. Selection of antipsychotics, particularly the newer ones require consideration of co-morbidities like obesity, diabetes mellitus and dyslipidaemias. During antipsychotic drug therapy periodic monitoring for metabolic abnormalities is advisable. It can be suggested that aripiprazole may be added to olanzapine therapy to prevent development of serious metabolic effect. A triple blind randomized trial for a long duration is required to make confident inference about the future of olanzapine.

REFERENCES:

1. Harrington C, Gregorian R, Gemmen E, Hughes C, Golden K, Robinson G *et al*. Access and utilization of new antidepressant and antipsychotic medications. Lewin Group: Falls Church, VA, 2000 (Accessed 17 June, 2014, at http://aspe.hhs.gov/search/health/reports/Psychmedaccess/index.htm#TOC).
2. Deutsch, A.Y. Mechanism of action of novel antipsychotic drugs; implications for novel therapeutic strategies for schizophrenia. Schizophr res 1991; 4: 121-56.
3. Haro J M, Salvador-Carulla L. The SOHO (Schizophrenia Outpatient Health Outcome) study: implications for the treatment of schizophrenia. CNS Drugs 2006; 20: 293–301.
4. Voruganti L, Switching from conventional to novel antipsychotic drugs: Results of prospective naturalistic study. Schizophr. Res., 2002, 57/2-3: 201-8.
5. Revicki, DA. Cost effectiveness of newer atypical antipsychotics: a review of pharmacoeconomics research evidence. Curr Opin Investig Drugs 2001; 2:110-17

6. Newcomer JW. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. J Clin Psychiatry 2007; 68(Suppl 1): 20–7.
7. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity. Diabetes Care 2004; 27: 596–601.
8. Casey DE, Haupt DW, Newcomer JW, Henderson DC, Sernyak MJ, Davidson M et al. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. J Clin Psychiatry 2004; 65 (Suppl 7): 4–18.
9. Goff DC, Sullivan LM, McEvoy JP, Meyer JM, Nasrallah HA, Daumit GL et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. Schizophr Res 2005; 80:45–53.
10. Newcomer JW. Medical risk in patients with bipolar disorder and schizophrenia. J Clin Psychiatry 2006; 67(Suppl9):25–30.
11. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. Br J Psychiatry 2000; 177: 212–7.
12. Meyer J M. Cardiovascular illness and hyperlipidemia in patients with schizophrenia. In: Meyer JM, Nasrallah HA (eds). Medical Illness and Schizophrenia. American Psychiatric Publishing Inc.: Washington DC and London, England, 2003, pp 53–80.
13. Gogia A, Agarwal PK. Metabolic syndrome. Indian J Med Sci 2006; 60: 72-81 (correspondence).
14. Nasrallah HA. The roles of efficacy, safety, and tolerability in antipsychotic effectiveness: practical implications of the CATIE Schizophrenia Trial. J Clin Psychiatry 2007; 68(Suppl 1): 5–11.
15. Citrome L. A review of aripiprazole in the treatment of patients with schizophrenia or bipolar I disorder. NeuropsychiatrDis Treat. Dec 2006; 2(4): 427–43.
16. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome: a new world wide definition.A concensus statement from the International Diabetes Federation. Diabet Med 2006; 23: 469-80.
17. Barnwal A, Oza B, Patel V. Metabolic side effects of antipsychotic agents: a prospective study in a teaching hospital. NHL Journal of Medical Sciences2012; 1: 23-6.
18. Kerwin R, Tyalor D. New antipsychotics: a review of their current status and clinical potential. CNS drugs 1996; 1:71-82.
19. Leucht S, Wahlbeck k, Hamann J and Kissling W. New generation antipsychotics versus low-potency conventional antipsychotics: A systemic review and meta-analysis. Lancet, 2003; 361/369: 1581-9.
20. Tripathi K D.Essentials of Medical Pharmacology, seventh edn. Jaypee Brothers Medical Publishers (P) Ltd: New Delhi;2013. p.446.
21. Stock E, McQuade R D, Marcus R, Jody D, Gharbia NA, Vanveggel S et al. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. J Clin Psychiatry. 2004; 65(Suppl 18):47–56.
22. Paul E. K J, Marcus R,ourkodimitris S, Ali M, Liebeskind A,Saha A,Ingenito G. A Placebo-Controlled, Double-Blind Study of the Efficacy and Safety of Aripiprazole in Patients with Acute Bipolar Mania. Am J Psychiatry 2003; 160:1651–8.
23. Hampt D. Differential metabolic effects of antipsychotic treatments. Eur neuropharmacol 2006; 16: S149-55.
24. Wirshing DA, Boyd JA, Meng LR, et al.The effects of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry 2002; 63:856-65.
25. Lizheng S. Prediction of metabolic monitoring among schizophrenic patients with a new episode of second generation antipsychotic use in the veterans. Health Administration 2009; 10: 1186/1417-244X-9-80.
26. Ritter LM. Weight gain and response to olanzapine treatment in schizophrenia. Biol Psychiatry 2000; 47: 488.
27. Sahoo S, Ameen S, Akhtar S. Metabolic syndrome in drug-naïve first episode psychosis treated with atypical antipsychotics. Aust N Z J Psychiatry 2007; 41: 629.
28. Gautam S, Meena P S. Drug-emergent metabolic syndrome in patients with schizophrenia receiving atypical (second-generation) antipsychotics.Indian J Psychiatry. 2011 Apr-Jun; 53(2): 128–33. doi: 10.4103/0019-5545.82537