CHAPTER 5

DISCUSSION
Schizophrenia is perhaps the most dramatic and tragic manifestation of mental illness known to mankind. The consequences of the illness for the individual affected, his or her family, and society in general are devastating (Sadock, BJ, Sadock VA and Ruiz P, 2009). The worldwide prevalence of schizophrenia estimates range between 0.5% and 1%. Age of first episode is typically younger among men -about 21 years of age, than women 27 years of age (Centre for Disease Control, July 2011). Schizophrenia is a clinical syndrome of variable, but profoundly disruptive psychopathology that involves disturbances in cognition, emotion, perception, thinking, and behaviour. It is well established as a brain disorder, with structural and functional abnormalities visible in neuroimaging studies and a genetic component, as seen in twin studies. Despite significant advances in understanding of the nature of the disease, its causes and underlying brain mechanisms are yet to be fully uncovered, hence schizophrenia remains a mighty challenge to psychiatry (Gattaz & Bussatto, 2009).

While existing antipsychotic treatments for schizophrenia are not completely satisfactory, they can substantially reduce disease burden and make a meaningful difference in the life of each individual patient (Tandon R. et al., 2008). The atypical antipsychotic agents share the clinical attributes of a broader spectrum of efficacy, lower risk of extrapyramidal side effects (EPS) and tardive dyskinesia (TD), compared to older conventional agents. They are chemically and pharmacologically distinct from one another, and each consequently has a unique side effect profile (Tandon and Jibson, 2003). Although the use of atypical antipsychotics offers many benefits and may reduce some of the factors related to the morbidity and mortality of schizophrenia, these drugs appear to be associated with varying degrees of metabolic adverse effects, such as weight gain, impaired glucose metabolism, dyslipidemia and in some cases, more serious morbidity, such as cardiovascular disease (Nasrallah HA, 2008).

As schizophrenia is a chronic disorder, staying on the drug is critical for successful treatment as compliance is a major problem. Thus determinants of ‘drug’s effectiveness’ in schizophrenia are not mere efficacy (symptom relief) and tolerability but are also in addition - normal functions restoration, relapse prevention and remission maintenance with resultant treatment adherence on long-term treatment (Lieberman JA et al, 2005). Schizophrenia treatment in the context of clinical trial is often substantially different from daily clinical practice. Factors such as cognitive function, antipsychotic side effects, patients’ attitudes to medication and subjective well being can all affect the results of treatment in real-life clinical practice. While randomised, placebo-controlled trials and open-label extensions can provide valuable information about the long-term efficacy and tolerability of newer antipsychotic agents, they cannot address all the...
variables that may affect treatment outcome (Gorwood P, 2006) Clinical trials of antipsychotics in schizophrenia patients include highly selected patient populations, not truly representative of the patients these drugs would be used for in ordinary practice. This has led to the concept of effectiveness into play. An effectiveness study may examine flexible dosing regimens, has a long follow-up period, and measure quality of life and functional outcomes (McDonagh et al., 2010). Noninterventional, naturalistic studies facilitate examination of current clinical practices and provide an understanding of the impact of the biopsychosocial aspects of schizophrenia (Dossenbach et al, 2008).

Some prospective, observational studies have added to the knowledge about differences and similarities between different atypical antipsychotics (Strous et al 2006, Umadevi P and Murugam S 2009). However, there is paucity of literature on prospective long-term studies related to the metabolic adverse effects and subjective well-being of the patients receiving atypical antipsychotic drug treatment in Indian patients. Looking to the above needs, the present study was conducted with an aim to examine effectiveness, subjective well-being and tolerability (with focus on metabolic effects) in schizophrenic patients belonging to wide and variegated socio-economic background. This prospective, observational study was conducted in out-patients diagnosed with schizophrenia (DSM-IV criteria) and undergoing antipsychotic monotherapy on the best possible clinical knowledge, judgement and experience of the attending psychiatrist. Those patients prescribed antipsychotic monotherapy in routine clinical practice with naturalistic treatment setting (without treatment regimen intervention) and agreeable for the biochemical (fasting blood glucose and lipid profile) tests were enrolled for 48-weeks observational follow-up.

**Baseline Demographic and Other Characteristics**

Out of 182 out-patients with schizophrenia (DSM-IV criteria) receiving atypical antipsychotic monotherapy (initiated/continued on risperidone or olanzapine or clozapine) who were screened, 14 patients not fulfilling selection criteria were excluded and 168 out-patients were enrolled. None of the 168 patients were switched over from some other antipsychotic. There were 100 males (59.52%) and 68 females (40.48%) with M:F ratio 1.51 and mean age of 34.43±10.21 (range 18–62) years. The three groups comprised risperidone 94 (55.95%), olanzapine 69 (41.07%) and clozapine 5 (2.98%) patients. Among 168 study participants at baseline, the new patients on study antipsychotics were risperidone group (Ris) 32 patients (34.04%), olanzapine group (Ola) 43 patients (62.32%) and clozapine group (Cloz) 0 patients (0.00%). The continuers patients who were already previously prescribed the study antipsychotics were Ris group 62 patients (65.96%), among Ola group 26 patients (37.68%) and among Cloz group all the 5 patients (100%). The gender distribution among three groups was: Ris group 57 males (60.64%) and 37 females.
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(39.4%); Ola group - 39 males (56.52%) and 30 females (43.48%) and Cloz group, 4 males (80.00%) and 1 female (20.00%). There was no statistically significant difference between three groups with respect to age and gender ($p > 0.05$). In a 12-week prospective naturalistic observational study by Strous et al (2006), 131 in- and out-patients with schizophrenia or schizoaffective disorder (DSM IV criteria) who were prescribed risperidone ($n=38$), olanzapine ($n=38$) and clozapine ($n=55$) with mean age of 35.4 ($SD = 10.9$), 34.6 ($SD = 12.2$) and 39.0 ($SD = 12.6$) respectively were comparable with mean age in risperidone group in present study 35.37 ($SD = 10.54$), but not comparable in case of olanzapine and clozapine groups. The Strous et al study participant’s gender segregation of 76 (58%) males and 55 (42%) females was comparable with that of present study [males - 100 (59.52%) and females 68 (40.5%)]. Although study participants in Strous et al, 2006 were in- and out-patients, all the three atypical antipsychotics used were same as used in present study.

Of 168 enrolled patients, those who were lost-to follow up (for unknown reason) before post-baseline scheduled assessment and/or study drug exposure were, Ris - 7 and Ola - 7 respectively. So the post baseline analytical sample consisted of 154 patients with Ris - 87, Ola - 62 and Cloz - 5 patients respectively.

**Effect of Atypical Antipsychotics on ‘Functioning’ and ‘Subjective well-being’**

In present study, based on mean GAF (Global Assessment of Functioning) score, the three drug groups showed comparative improvement in overall functioning with endpoint mean scores for Ris ($63.76 \pm 9.20$), Ola ($63.39 \pm 7.97$) and Cloz ($68.60 \pm 5.32$) compared to baseline mean scores of $53.66 \pm 2.11$, $53.15 \pm 2.02$ and $53.2 \pm 2.49$ respectively without statistically significant difference between three groups ($p > 0.05$). In a 6-month prospective, comparative, observational, naturalistic study by Garcia-Cabeza I et al (2001) in outpatients with schizophrenia, the baseline mean GAF scores reported in risperidone ($n=417$) group was $46.7 \pm 14.6$ and in olanzapine ($n=2128$) group was $44.9 \pm 14.8$, which are lower than found in the present study as $53.66 \pm 2.11$ with risperidone group and $53.15 \pm 2.02$ with olanzapine group respectively. No mention of study endpoint GAF score is done by Garcia-Cabeza I et al (2001). The findings of present study of comparable overall functioning assessed by GAF in olanzapine and risperidone are in accordance with those reported in a 6-month prospective, comparative, observational, naturalistic study in 182 patients with schizophrenia by Montes JM et al, 2003.

After the introduction of the first antipsychotic, chlorpromazine, many patients complained of an altered subjective state labeled as neuroleptic dysphoria. The consequences of neuroleptic dysphoria and lack of subjective tolerability such as their negative impact on adherence behaviour and on eventual outcomes such as frequent relapses, excessive utilization of resources, hospitalizations, and compromised quality of
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life (QOL) were increasingly recognized in clinical research (Awad & Voruganti, 2004). Generic (nonspecific) tool for QOL have been used in some studies as reported by Solanki et al (2008) in cross-sectional study of 50 schizophrenic out-patients assessed for influence of clinical and sociodemographic factors on their QOL investigated by self-reported WHO QOL - BREF scale The Patients were having lowest QOL scores in social relationships domain of the scale There were no statistically significant correlation between QOL parameters and clinical characteristics in schizophrenics. Scores on positive subscale and total PANSS were significantly negatively correlated with physical, psychological, social relationship domains and total QOL Negative subscale had significant negative correlation with physical and psychological domains and total QOL. General psychopathology subscale had significant negative correlation with all subscales of QOL This study demonstrated a poor QOL in schizophrenia despite significant improvement with pharmacological treatment.

Several factors can affect functional and subjective outcomes Among them are premorbid functioning, psychopathological symptoms, insight and attitude toward disease and treatment, and side-effects of medication (Hofer A, 2006) Subjective well-being is a major component of quality of life (QOL), influenced by the pharmacological and/or psychosocial treatment as well as by the illness itself The impact of antipsychotic drugs on subjective wellbeing, together with the quality of the doctor–patient relationship, is one of the two agreed major determinants for medication compliance. Studies on subjective well-being (SW) disproved the former belief that schizophrenic patients are not able to reliably assess their SW. The majority of schizophrenic patients, if not acutely psychotic or suffering from severe cognitive impairment, are able to complete self-rating scales in a consistent and reliable manner (de Millas et al., 2006) Subjective Well-Being Under Neuroleptic Treatment Scale, a 20-item (SWN-20) scale (also known as SWN-K scale) is a disease-specific scale. SWN score and its subscores [five domains (regarding mental or cognitive functioning, self-control, emotional regulation, physical functioning and social integration, and each of the five domains and their two (positive and negative) domains] appear to correlate with measure of objective psychopathology, quality of life and other self-ratings of mood. It is a self-reported (patient-reported) scale developed to assess the subjective well-being of patients receiving antipsychotic medication Past research indicates that quality of life, much more improved by atypical than by typical antipsychotics, has a strong impact on compliance, as well as on the chance of achieving remission (Walter de Millas et al., 2006) The SWN-20 tool has demonstrated good practicability, reliability, validity and sensitivity (Naber, 2001 and 2005, Schmidt P et al, 2006, Siamouli M et al, 2009) Hence SWN-20 scale was used in the present study as a measure of evaluation of disease-specific QOL in participants.
A large noncomparative postmarketing study of schizophrenia patients treated with risperidone by Jeste et al (1997) reported significant improvement in QOL in 58% of patients by week 10, compared with only 25% at baseline. In another long-term study by Bobes et al (1998), 362 schizophrenia patients were switched from other antipsychotics to risperidone. Improvement in QOL was reported following 8 months of treatment. Several studies comparing the impact of risperidone and olanzapine on QOL indicated similar improvement in both groups (Tran et al 1997, Ho BC et al 1999, Revicki et al 1999). Other comparative studies concluded that patients taking olanzapine demonstrated more improvement in QOL, compared with those taking haloperidol (Hamilton et al, 1999). Several studies reported the superiority of clozapine to first-generation antipsychotics in improving QOL for treatment-refractory schizophrenia patients (Meltzer et al 1990 and 1995, Rosenheck et al 1997, Naber et al 2001, Awad & Voruganti, 2004).

In a study by de Haan et al (2000) it was shown that dosage of medication leading to dopamine (D$_2$) receptor blockade should be carefully evaluated, since it is most likely responsible for neuroleptic dysphoria, even in the absence of motor side effects. The relationship between SWN score and striatal D$_2$ receptor occupancy was investigated in 22 schizophrenic patients, clinically stable under either 14.7 mg of olanzapine or 4.1 mg of risperidone. It was demonstrated that in the absence of extrapyramidal symptoms, higher striatal D$_2$-receptor occupancy as measured by single photon-emission computed tomography (SPECT) was related to reduced SWN, negative symptoms, and depression (P< 0.01) (de Millas et al., 2006).

An observational study aimed to evaluate the QOL of patients on different antipsychotics as monotherapy using SWN and DAI-30 scales found no significant difference between different antipsychotics namely clozapine, olanzapine, quetiapine, risperidone and haloperidol (Balestren M et al, 2009). While most of quality of life studies have methodological and design limitations, the weight of evidence from them nevertheless points to a trend towards a more positive impact on quality of life with atypical agents (Awad & Voruganti, 2004). In a recent review of antipsychotics by McDonagh et al., 2010, good-quality trials evidence did not differentiate olanzapine, quetiapine, risperidone, or ziprasidone in quality-of-life measures, although improvements were seen with all the drugs. Observational evidence is mixed with some indicating a potential for olanzapine to result in larger improvements depending on the scale used. Limited evidence from a single trial found olanzapine to result in better social function compared to risperidone, however, observational evidence conflicts with these findings (McDonagh et al., 2010).

In present study, there was no statistically significant between-group difference between three drug groups in SWN-20 total score or its five positive and five negative domains at baseline or endpoint (except...
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In case of physical functioning negative score at baseline – between risperidone and clozapine and between olanzapine and clozapine) In case of within-group difference in three groups, in SWN total score as well as in its other nine subdomains, there was statistically significant difference between baseline score and endpoint score, except in case of mental functioning positive score (domain) in clozapine group. This shows progressive improvement in all domains of subjective wellbeing in study participants receiving risperidone, olanzapine and clozapine except in case of mental functioning positive domain in clozapine group. The findings of present study (n=154) of comparable subjective wellbeing improvement at endpoint compared to baseline in olanzapine group (n=62) and clozapine group (n=5) with no significant between-group difference are in accordance with the findings of a 26-week randomized controlled trial (n=114) by Naber et al, 2005 which showed olanzapine group (n=57) and clozapine group (n=57) comparable with respect to subjective wellbeing improvement at endpoint compared to baseline without statistically significant between-group difference as olanzapine was found non-inferior to clozapine (Naber et al, 2005)

Efficacy of Atypical Antipsychotics

(1) Efficacy measured by - PANSS (Positive and Negative Syndrome Scale) Score and Response Rates (percentage improvement on PANSS Total Score at endpoint compared to baseline)

As reported in a comprehensive review on Indian research in schizophrenia by Kulhara P et al, 2010, in small open trials, Agarwal AK et al (1998), Agashe M et al (1999) and Krishnan S et al (1999) found that risperidone was both efficacious and safe as an antipsychotic. Agarwal and Chadda (2001) also found in 44 patients with schizophrenia that once daily risperidone was as efficacious as twice daily risperidone. Of the twenty one Indian studies published between 1997 and 2010 on evaluation of the efficacy/effectiveness of atypical antipsychotics in schizophrenia, twelve have reported the efficacy of risperidone, five of clozapine, two of olanzapine, two of aripiprazole and one of quetiapine. Some of these studies have also evaluated different doses of the same medications and some others have evaluated the dosing schedule. All these trials have included subjects diagnosed as schizophrenia on the basis of DSM-IV or ICD-10 except for Agashe (1999) who used DSM-IIIR criteria. All these trials used standard instruments to assess the efficacy and side effects. The sample size varied from 24 to 606 and the duration of these trials have been six weeks to four months except for one trial which evaluated the outcome on risperidone at one year (Shrivastava A and Gopa S, 2000) and two studies, which followed up subjects on clozapine for 20 months and three years respectively (Shrivastava S et al 2002, Raguraman J 2005). Agarwal and Chadda (2001) demonstrated that there was no difference in efficacy of once daily dose versus twice daily dose of risperidone. The study by Shrivastava A and Gopa S, 2000 which followed up the subjects on risperidone for one year showed that compared to haloperidol, more subjects on risperidone had better social
functioning, productivity and education and significantly fewer patients had suicidal ideation or attempts and needed rehospitalization.

Clozapine was tested by Desai et al (1999) in treatment resistant cases and 25-50 % decline in the BPRS score was noted, and sedation and sialorrhea were seen to be the most common side-effects. An open clinical trial on clozapine was conducted in a group of treatment resistant patients by Agarwal et al (1997). Raguraman et al (2005) evaluated the effectiveness of clozapine in 22 treatment resistant schizophrenic patients, following them up for 20 months and found that the study group showed better global functioning and decline in suicidal thoughts, negative symptom and general psychopathology scores on PANSS. All the studies which have evaluated clozapine have done so in TRS (treatment-resistant schizophrenia) cases and have reported it to be useful in both short and long term (Kulhara P et al, 2010).

As reported in another review on antipsychotics in India by Avasthi A et al, 2010, Srivastava et al (2001) showed that half of the schizophrenia subjects in India require 3-4 mg/day of risperidone and another one-third improve with dose ranging from 1-2 mg/day. All the studies on risperidone have shown that it is efficacious in short term. Avasthi et al (2001) in a small open trial compared olanzapine with haloperidol and found that olanzapine was equally efficacious to haloperidol in improving overall psychopathology and positive symptoms, and had superior efficacy in improving negative symptoms and secondary depressive and anxiety symptoms. Thomas et al (2008) reported that there was significant improvement in PANSS total, negative and general psychopathology scores and also in CGI-S and CGI-I scores at 6 weeks with olanzapine treatment.

Response rates across the atypical antipsychotics range widely across trials, due to variations in patient populations, duration of follow-up, and definition of response. Across the trials, statistically significant differences in response rates were very rare, with these differences occurring only when data were analyzed according to multiple definitions of response or when only patients completing a 12-month trial period were included. In these cases, however, other analyses or other trials have not confirmed findings of a difference. Four trials comparing olanzapine with risperidone reported response rates of atypical antipsychotics on PANSS total scale. Each of these trials reported response rates of > 20% on the PANSS scale, but only the Gureje study found a statistically significant difference on this measure between two drugs (olanzapine 75%, risperidone 47%, P=0.01). Pooling results of this smaller study with the other short-to-medium-term trials showed no significant difference between the drugs. Tran (1997), Gureje (2003), and Conley (2001) also reported response rates defined as > 40% improvement on the PANSS. Tran found the difference was just statistically significant (P=0.049), favoring olanzapine, Gureje found no difference, and
Conley found risperidone superior \((P<0.03)\). Pooling of data from three studies does not show a significant difference across two antipsychotic groups \((P=1.07, 95\% \text{ CI 0.59 to 1.93})\).

The results of present study show overall progressive decrease in mean score values in case of total PANSS score as well as in its subscales (PANSS positive, negative, and general psychopathology) clozapine, olanzapine and risperidone groups respectively. Statistically significant within-group difference in PANSS total score in three groups between baseline, quarterly time-points (week 12, week 24, week 36), and endpoint data \((p < 0.05)\) was found. The between-group statistical difference in three groups was found at baseline (between risperidone and olanzapine, and between risperidone and clozapine, but not between olanzapine and clozapine). No between-group statistical difference in three groups was found at endpoint. The present study findings of overall progressive decrease in PANSS total score and its subscores are consistent with a 12-week long prospective naturalistic observational study by Strous R D et al (2006) comparing risperidone \((n=38)\), olanzapine \((n=38)\) and clozapine \((n=55)\) in inpatients and outpatients with schizophrenia and schizoaffective disorder (DSM IV), all patients showed a significant decrease in PANSS total score and its subscores - Positive, Negative and General Psychopathology scores over the period of 12 weeks, without between-group comparable difference.

In present study, different PANSS response cut-offs assessed at endpoint found the following: PANSS Reduction of \(\geq 20\%\): Clozapine \((n=5, 100\% \text{ patients})\), Olanzapine \((n=45, 72.6 \% \text{ patients})\), Risperidone \((n=59, 67.8 \% \text{ patients})\). Among other Response Rates assessed: PANSS Reduction \(\geq 30\%\). Clozapine \((n=3, 60\% \text{ patients})\), Olanzapine \((n=31, 50\% \text{ patients})\), Risperidone \((n=40, 46\% \text{ patients})\), PANSS Reduction \(\geq 40\%\). Clozapine \((n=1, 20\% \text{ patients})\), Olanzapine \((n=4, 645\% \text{ patients})\), Risperidone \((n=2, 2.3\% \text{ patients})\); No patient showed PANSS response \(\geq 50\%\) The findings of present study are in line with the findings of Gureje et al, 2003 indicating PANSS response rate higher than \(\geq 20\%\) in case of olanzapine compared with risperidone. The smaller sample size \((n=5)\) in clozapine group should be taken in to account while looking at these findings.

The ‘percentage (%) change in PANSS total score’ among three therapeutic groups at endpoint compared to baseline were not significantly different \((p = 0.219)\) Thus all three drug groups were found to have comparative improvement at endpoint over the period of 48 weeks irrespective of baseline psychopathological scores.

As far as correlation between SWN-20 and PANSS scores is concerned it was found that, except SWN-mental functioning and physical functioning positive and negative scores, rest of the statistically significant correlations between SWN-20 and its subscales and PANSS and its subdomains were having moderate to
very strong, negative or inverse correlation. It shows that the assessment of patient-rated SWN-20 and of clinician-rated PANSS are not strongly related. This indicates that the assessment of subjective well-being under antipsychotic treatment made by patients and assessment of psychopathology made by clinicians differ. This is in accordance with the findings of a double blind clinical trial of olanzapine and clozapine that the effects of antipsychotic treatment on subjective well-being (SWN) correlated only moderately with their effects on psychopathology (PANSS), with a correlation coefficient of \( r = -0.45 \) indicating that patients and psychiatrists perceive treatment differently (Naber et al. 2005).

(2) **Efficacy in terms of Global Clinical Status measured by Clinical Global Impression-Severity and Improvement (CGI-S and CGI-I) Scale**

With respect to CGI-S score, analysis of our data showed the change in mean CGI-S score from baseline over a study period of 48 weeks as follows: Clozapine 1.0, Risperidone 0.59, Olanzapine 0.55. There was no between-group statistical difference among three groups at baseline or at endpoint. However, there was significant within-group difference in three groups between baseline, quarterly time-points (week 12, week 24, week 36), and endpoint data \( (p < 0.05 \) in three groups) except in case of clozapine group between baseline & 12 week, and between baseline & 24 week CGI-S data, suggesting the progressive improvement (reduction in illness severity) by three drugs at endpoint over the period of 48 weeks. With respect to CGI-I (CGI improvement) score, analysis of data showed the change in mean CGI-I score from baseline over a study period of 48 weeks as follows: Clozapine 1.8, Olanzapine 1.27, Risperidone 1.22. There was no between-group statistical difference among three groups at baseline or at endpoint. However, there was significant within-group difference in three groups between baseline, quarterly time-points (week 12, week 24, week 36), and endpoint data \( (p < 0.05 \) in three groups), suggesting the progressive improvement in three drugs at endpoint over the period of 48 weeks.

The 'percentage (%) change' in CGI-S and CGI-I scores among three therapeutic groups at endpoint compared to baseline were not significantly different \( (p = 0.182 \) and \( p = 0.219 \) respectively). Thus all three drug groups were found to have comparative improvement at endpoint over the period of 48 weeks. The pattern of progressive change in CGI score was similar to that found with change in PANSS score.
Discussion

Tolerability of Atypical Antipsychotics

There have been very few Indian studies reported to examine the long-term effects of atypical antipsychotics on tolerability including different metabolic parameters

(1) Effect of Atypical Antipsychotics on Weight and BMI:

There is compelling evidence that patients with schizophrenia are prone to gain weight. In addition, atypical antipsychotic (AAP) drugs also induce weight gain. All antipsychotic drugs produce weight gain but the potential varies (Ananth J et al., 2004). Atypical antipsychotics (AAPs) differ in their ability to induce weight gain, and in the duration of this effect. This presumably reflects differences in their pharmacological properties, and calls into question the mechanisms by which these agents act on body weight regulation. At present, these remain unclear, although it seems likely that multiple mechanisms are involved (Chue P and Cheung R, 2004). Weight gain is associated with an increased risk of diabetes mellitus and hyperlipidemia (all associated with an increased risk of coronary heart disease), and there are increasing reports of these complications in patients with schizophrenia receiving atypical antipsychotics (Tandon and Jibson, 2003).

In one of the most cited comprehensive review of research literature by Allison DB et al (1999) estimated mean weight change calculated using both fixed and random effects models. For patients on standard doses for 10 weeks, the authors calculated point estimates of weight gain for each drug. Weight gain associated with five atypical antipsychotics was examined in the study – ziprasidone (0.04 kg), risperidone (2.10 kg), sertindole (2.92 kg), olanzapine (4.15 kg) and clozapine (4.45 kg). Weight change induced by risperidone was intermediate between the group of antipsychotics associated with low or no risk of weight gain (molindone -0.39 Kg; ziprasidone +0.04 kg) and the group of drugs associated with high risk (thioridazine +3.19; olanzapine +4.15 kg, clozapine +4.45). Subjects receiving placebo lost weight in the range of 0.74 kg. Though the two typical antipsychotics molindone and pimozide were associated with weight loss, the effects were not significant at 10 weeks. The study indicated that patients may gain more than 5% of initial body weight, with the weight gain becoming more pronounced with time, with the attendant risks for the general physical health of the patient.

In an Indian double-blind prospective study by Saddichha S et al (2007) in previously drug-naive schizophrenia patients, 31.81% prevalence of obesity, 10.1% incidence of obesity (Saddichha S et al, 2008a), and 18.2% prevalence of metabolic syndrome (Saddichha S et al, 2008b) after 6-weeks of treatment with antipsychotics based on waist circumference has been reported (Padmavati R, 2010). Weight change was observed in 80 outpatients receiving olanzapine by Jain et al (2006) with 66.6% of the...
patients had weight gain over a period of 4 weeks which was not related to the dose of the drug or BMI. In present study, the waist circumference measurement was not feasible for the reason explained under limitations. In present study, the weight changes and obesity were defined based on the revised BMI cut-offs (kg/m²) in Asian Indians as per Misra A et al (2009): Normal. 18 to 22.9, Overweight. 23 to 24.9 and Obese > 25 kg/m²

In present study, of 154 study participants analysed, mean weight gain associated with olanzapine group (3.2 kg) was higher followed by clozapine (2.6 kg), and modest weight gain with risperidone (1.57 kg). The mean BMI changes were consistent with changes in mean weight gain and found to be higher in olanzapine group (1.31 kg/m²) followed by clozapine (1.00 kg/m²) and risperidone (0.61 kg/m²) groups. Further between-group statistical analysis both in case of weight and BMI parameters showed that although risperidone and olanzapine groups differ statistically significantly at endpoint (compared to baseline), clozapine group does not differ from either of two (olanzapine and risperidone) groups in weight gain and BMI at endpoint (compared to baseline).

The percentage of patients with clinically significant bodyweight gain of >7% compared with baseline in the CATIE study (Lieberman JA et al., 2005), among antipsychotic drugs reported was 30% and 14%, for olanzapine and risperidone respectively. In pivotal trials reviewed by Allison and Casey (2001), it was reported as 29% and 18%, for olanzapine and risperidone respectively. In present study over a study period of 48 weeks, it was 26(42%), 1(20%) and 15(17.24%) patients for olanzapine, clozapine and risperidone respectively. Among these patients with clinically significant weight gain at endpoint, there was preponderance in patients with normal BMI- 24(15.6%) followed by obese BMI- 9(5.84%) patients. There was no significant difference between three treatment groups in this respect (p > 0.05). Although smaller sample power in case of clozapine (n=5) requires consideration, present study findings corroborate with the previous reports indicating weight gain potential to be more often associated with olanzapine and clozapine, and comparatively modest weight gain with risperidone among atypical antipsychotics (Allison DB et al 1999, Strous RD et al 2006).

Tandon and Jibson (2003) have reported the weight gain potential of atypical antipsychotics as: clozapine > olanzapine > risperidone = quetiapine > ziprasidone = anipiprazole. Weight gain associated with five atypical antipsychotics was examined by Allison DB et al (1999) was ziprasidone (0.04 kg), risperidone (2.10 kg), sertindole (2.92 kg), olanzapine (4.15 kg) and clozapine (4.45 kg) revealing weight change induced by risperidone to be intermediate. In a 12 week-long prospective naturalistic observational study comparing risperidone (n=38), olanzapine (n=38) and clozapine (55) in inpatients and outpatients, Strous RD et al
(2006) observed that clozapine-treated patients showed greater increase (from baseline) in proportional weight change compared to olanzapine and risperidone (both $p < 0.05$). In a recently reported 12 week-long prospective observational study reported by Barnwal A et al (2012), 45 outpatients receiving typical and atypical antipsychotics were screened with varied psychiatric diagnosis, of which 12 were withdrawn and 33 were followed up. At the end of the study, all the antipsychotics showed statistically significant weight changes with olanzapine +7.38 kg but risperidone -4.237 kg.

In a naturalistic study by Ganguli R et al (2001) changes in body weight and BMI in 100 patients treated for 4 months with risperidone or olanzapine were compared. There was no significant change in either measure in risperidone-treated patients while the patients receiving olanzapine showed a mean weight gain of approximately 2 kg from baseline, and a significant increase in BMI. In a prospective study by Conley and Mahmoud (2001), 377 patients received flexible doses of risperidone 2–6 mg, or olanzapine 5–20 mg, for 8 weeks. Risperidone was associated with significantly less weight gain than olanzapine (mean 1.5 vs. 3.3 kg, respectively, $P<0.001$), and significantly fewer patients experienced a weight gain of 7% or more with risperidone (12% vs. 27%, $P<0.001$). Moreover, in risperidone-treated patients, weight gain was mainly seen in patients with a low body mass index (BMI) at baseline, whereas with olanzapine weight gain occurred irrespective of the patients’ baseline BMI (Chue P and Cheung R, 2004). These findings show higher weight gain potential of olanzapine than risperidone as in the present study.

The possible involvement of other factors which can contribute to weight gain such as chronic medication treatment regardless of type, underlying illness features predisposing to weight gain over time or illness features that require exposure to antipsychotic medication along with underlying predisposition to significant weight gain over time need consideration (Ananth et al., 2004).

**Effect of Atypical Antipsychotics on Fasting Blood Sugar**

In present study, although there was significant between-group difference among risperidone and clozapine groups ($p=0.041$), and between olanzapine and clozapine groups ($p=0.011$) at the endpoint, no significant within-group difference was found between baseline, week 12 and endpoint data in any of the three groups ($p > 0.05$). There were no cases with ‘high’ (clinically significant) FBG changes (≥ 126 mg/dL) at baseline, week 12 and endpoint in any of the three drug groups. However, ‘borderline’ FBG changes (>100 to <126 mg/dL) were observed in three drug groups. At baseline total 11(7.14%) cases of which in risperidone 8 cases followed by clozapine 2 and olanzapine 1 case. At week 12, the total 12(7.8%) cases - Ris 6 cases, Ola 5 and Cloz 1 case. At endpoint, total 14(9.1%) cases - Ris 8 cases followed by olanzapine 4
and in clozapine 2 cases. Thus the FBG changes were not consistently seen with these drugs in study participants.

These findings, related to fasting blood glucose, are consistent with the findings of Ingole et al, 2009 [104.73(SD 1.850)] and Barnwal et al, 2012 [86.21(SD 3.19)] in which regardless of statistically significant changes found in FBG at the study endpoint, they were still within clinically normal range (below 126 mg/dL). In a randomized open-label study of 12 weeks of patients with schizophrenia, Ingole S et al, 2009, observed that mean body weight and BMI were significantly increased from baseline to 6 and 12 weeks in both olanzapine (n=30) and risperidone (n=30) groups (P<0.001). The mean blood sugar was found to be significantly elevated after 6 and 12 weeks of treatment with olanzapine (P<0.001) but not in risperidone group. However, regardless of statistically significant changes in FBG by olanzapine at the study endpoint, they were still within clinically normal range [104.73(SD 1.850)] (below 126 mg/dL). In a 12 week-long observational study reported by Barnwal A et al (2012), 45 outpatients receiving typical and atypical antipsychotics were screened with varied psychiatric diagnosis. Of these 12 were withdrawn and 33 were followed up. At the end of the study, regardless of statistically significant changes found in FBG at the study endpoint, they were still within clinically normal range [86.21(SD 3.19)] (below 126 mg/dL).

The present study findings are in contrast with other studies and reviews which focused on metabolic effects of atypical antipsychotics (Henderson et al. 2000, Strous et al 2006, Umadevi P and Murugam S 2009, Koro CE et al 2002a, Llorente and Urrutia, 2006). In a 12 week-long prospective naturalistic observational study by Strous R D et al (2006) comparing risperidone (n=38), olanzapine (n=38) and clozapine (55) in inpatients and outpatients, the patients treated with clozapine showed greater increase compared to other drugs (olanzapine and risperidone) with respect to fasting blood glucose ($x^2=5.99$, df=2, $p=0.05$). An Indian observational study conducted by Umadevi P. and Murugam S, 2009 to focus on metabolic disturbances which comprehensively examined metabolic parameters viz weight/BMI, serum glucose and serum lipids together, conducted in 60 schizophrenic in-patients of age group 18-65 years of both sexes. It reported increase in blood glucose levels in schizophrenic patients treated with antipsychotic drugs. However, it was a hospital based study consisting in-patients belonging to good socioeconomic background. In a five year naturalistic study of 82 patients treated with clozapine (Henderson et al. 2000), weight gain and onset of diabetes were studied at 6 monthly intervals. Thirty (36.6%) patients developed diabetes, with 43 (52.4%) patients of the study population experiencing at least one episode of elevated fasting blood glucose ≥ 140 mg/dL. Serum triglycerides increased significantly as well. The limitations of the study included not being able to examine the role of risk factors such as ethnicity, family history or exercise. Koro et al (2002), in a large population-based, case-control study, found the risk of diabetes associated with antipsychotics to be
Discussion

quite variable. Olanzapine had 4.2 times the risk associated with typical agents and 5.8 times the risk associated with no treatment. Risperidone had 1.6 times the risk of typical drugs and 2.2 times the risk associated with no treatment. Several large population retrospective studies have found that olanzapine and clozapine are associated with a significantly higher rate of diabetes than other atypical antipsychotics risperidone and quetiapine. The risk of diabetes, however, is higher with antipsychotic treatment use than in a general patient population sample (Fuller MA et al, 2003; Llorente and Urrutia, 2006).

Of note, schizophrenia is an independent risk factor for diabetes (Krishnadev et al, 2008). The higher diabetes occurrence among schizophrenic patients is ascribed to traditional risk factors which are not directly associated with effects of the antipsychotics (such as genetics, physical inactivity, unhealthy nutrition). They cumulatively influence the insulin resistance, and eliminating some of them enables a safer use of the antipsychotics (Filakovic, 2012). In the Indian context, ethnicity, diet and lifestyle differences are likely to influence insulin sensitivity (Padmavati R, 2010). As reported by various comorbidity studies, lifestyle changes and weight gain are among the possible factors to be associated with type 2 diabetes in addition to factors such as schizophrenia itself, its genetic factors and antipsychotic medication (Juvonen H, 2007). The education, diet control and simple behavioral measures may prevent excessive weight gain (Ananth et al, 2004), which is reported to be one of the contributing factors for type 2 diabetes (Juvonen H, 2007).

Effect of Atypical Antipsychotics on Fasting Lipid Profile

Case series have played an important role in highlighting the increased prevalence of hyperlipidemia associated with atypical antipsychotic use. A retrospective case series of 14 psychiatric patients by Meyer (2001) reported that although BMI and weight increased for all patients, hyperlipidemia was not correlated with weight gain, change in BMI, use of lithium or valproate or previous history of hyperlipidemia. In a five year naturalistic study of 82 patients treated with clozapine (Henderson et al. 2000), weight gain and onset of diabetes were studied at 6 monthly intervals. Thirty (36.6%) of patients developed diabetes. Serum triglycerides increased significantly as well. The limitations of the study included not being able to examine the role of risk factors such as ethnicity, family history or exercise. In a comparative study by Wirshing DA et al (2002), treatment with various antipsychotics resulted in significantly elevated triglyceride levels in 56% of clozapine, 39% of olanzapine and 21% of risperidone-treated patients compared to none of haloperidol and 8% of fluphenazine-treated patients. The same study showed a reduction of HDL cholesterol during treatment with clozapine and olanzapine, whereas total cholesterol levels were significantly lower in risperidone- and fluphenazine-treated patients. A large retrospective case-control
study from the United Kingdom by Koro et al (2002) assessed the effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in 18,309 patients with schizophrenia. Olanzapine users had a significantly increased risk of hyperlipidemia compared with patients receiving typical antipsychotics (3.36-fold increase in risk) or no antipsychotic exposure (4.6-fold increase in risk). In contrast, risperidone was not associated with an increased risk of hyperlipidemia compared with typical antipsychotics or no exposure.

In one of the most cited review the hyperlipidemic potential of atypical antipsychotics is reported as follows: clozapine > olanzapine > quetiapine ≥ risperidone > ziprasidone = aripiprazole (Tandon and Jibson, 2003). Saari et al. 2004 suggested that the pathogenesis of hyperlipidemia is related to weight gain, with accumulation of abdominal fat increased release of free fatty acids in the liver and accelerating hepatic triglyceride synthesis as well as very low density lipoprotein (VLDL) release. They further suggest that increased lipids impair glucose metabolism, leading to hyperglycaemia and type-2 diabetes mellitus.

Several studies have demonstrated hyperlipidemia, especially hypertriglyceridemia, in patients who also showed glucose dysregulation during treatment with clozapine and olanzapine. Furthermore, hyperlipidemia, and especially hypertriglyceridemia, may itself be associated with insulin resistance (and secondary increased insulin secretin) (Ferraoli et al. 2004). An increase of serum lipid levels was seen after 4 weeks of treatment with olanzapine or clozapine and was significantly correlated with increasing BMI (Rettenbacher MA et al., 2006).

A prospective study by Wu RR et al (2006) comparing the effects of the second generation antipsychotics clozapine, olanzapine, risperidone and the first generation antipsychotic sulpiride on glucose and lipid metabolism in first-episode schizophrenia at baseline and 8 weeks after inclusion showed that besides higher C-peptide, fasting insulin and insulin resistance index (IRI), cholesterol and triglyceride levels were significantly increased in the clozapine and olanzapine groups. Because of these results the authors recommend that baseline and 6-month monitoring of fasting blood glucose, fasting cholesterol and triglyceride levels should be obtained in routine clinical practice with all antipsychotics to monitor the risk for development of hyperglycaemia and hypercholesterolaemia.

In 12 week-long prospective naturalistic observational study comparing risperidone (n=38), olanzapine (n=38) and clozapine (n=55) in inpatients and outpatients, Strous R D et al (2006) observed that patients treated with clozapine showed greater pathological change compared to other drugs with respect to triglycerides (χ²=9.57, df=2, p=0.008). Risperidone patients tended to exhibit reduced cholesterol levels. However, no statistically significant difference between the medications was noted with respect to
cholesterol Murashita M et al (2007) in a naturalistic study in 15 stable schizophrenic patients on chronic risperidone monotherapy compared with 25 healthy controls examined the effect of risperidone on fasting blood glucose, insulin, HbA1c, growth hormone, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, leptin, total ghrelin, active ghrelin and prolactin in addition to body weight, BMI, body fat percentage, clinical symptomatology, global functioning and quality of life. There were statistically significant changes at biochemical level with respect to FBG, triglycerides, HDL-cholesterol, leptin, total ghrelin, active ghrelin and prolactin (all $p < 0.05$). There were near significant changes in case of LDL-cholesterol ($p = 0.0513$) Also there was significant change in BMI and body fat percentage. The mean dose of risperidone used ($2.6 \pm 1.1$ mg/day, range 1-5 mg/day) in stable schizophrenics by Murashita M et al was lower than used in our present study ($4.76 \pm 1.5$ mg/day, range 1-8 mg/day used at endpoint).

In November 2003, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity convened a consensus development conference on the subject of antipsychotic medications and diabetes and obesity ADA/APA/AACE/NAASO (2004) consensus statement (commonly known as ADA/APA consensus guidelines) have recommended stringent monitoring of metabolic status and cardiovascular risk factors in psychiatric patients receiving antipsychotic medications. The ADA/APA guidelines is one of the most often cited published guidelines and has a broad medical representation and a practical monitoring structure useful to clinicians that fulfills most of the established monitoring goals (Gill JS et al, 2012).

There are two Indian observational studies that focus on metabolic disturbances. Umadevi and Murugam (2009) examined metabolic parameters viz. body weight and BMI, serum glucose and serum lipids in 60 schizophrenic in-patients of age group 18-65 years of both sexes. They reported increased total cholesterol and triglyceride levels in schizophrenic patients treated with antipsychotic drugs. However, it was hospital based study consisting in-patients belonging to good socioeconomic background. In a 12-week-long observational study reported by Barnwal A et al (2012) olanzapine was found to be associated with statistically significant increase in total cholesterol and triglycerides and decrease in HDL-C, whereas risperidone and haloperidol were associated with statistically significant increase in triglycerides.

In present study, the change in mean values (mg/dL) of lipid parameters from baseline over a study period of 12 weeks in three groups were observed as follows: Total cholesterol: Risperidone (12.56) > Clozapine (4.92) > Olanzapine (-0.62, negative change), LDL Cholesterol: Risperidone (10.89) > Clozapine (0.95) > Olanzapine (-1.8, negative change), Triglycerides: Olanzapine (6.67) > Clozapine (6.32) > Risperidone (3.8),
HDL-Cholesterol: Clozapine (-0.54) > Olanzapine (-0.07) > Risperidone (0.76, increase). The change in mean values (mg/dL) of lipid parameters from baseline over a study period of 48 weeks (at endpoint) in three groups were observed as follows. Total cholesterol: Risperidone (6.89) > Clozapine (6.7) > Olanzapine (-0.04, negative change), LDL Cholesterol: Clozapine (8.94) > Risperidone (7.19) > Olanzapine (-0.05, negative change), Triglycerides: Clozapine (12.54) > Olanzapine (3.84) > Risperidone (0.01), HDL-Cholesterol: Clozapine (-6.28) > Olanzapine (-0.89) > Risperidone (-0.18)

Further statistical analysis of lipids data showed no significant between-group difference among three groups at baseline or endpoint in case of total cholesterol, triglycerides, LDL-Cholesterol and HDL-Cholesterol. However, within-group comparison, in case of risperidone group, between baseline and 12 weeks showed statistically significant difference in total cholesterol and LDL-cholesterol, whereas between baseline and endpoint there was statistically significant difference for LDL-cholesterol but not for total cholesterol. No within-group statistically significant difference was found in any of the three groups between baseline and 12 weeks or between baseline and endpoint for triglycerides and HDL-cholesterol.

In addition to statistical analysis mentioned above, clinically significant biochemical changes considering TC (≥240 mg/dL), LDL-C (≥160 mg/dL) and TG (≥200 mg/dL), and borderline changes considering TC (200 to 240 mg/dL), LDL-C (130 to 159 mg/dL) and TG (150 to 199 mg/dL) in three groups were examined at corresponding follow-up laboratory evaluation visits, at 12 weeks and at endpoint (48 weeks) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001 NCEP-ATP-III, and American Diabetes Association, 2010).

At week 12, lipid changes were observed in 42 participants (Ris 23, Ola 17, Cloz 2) of which, the occurrence of 'clinically significant' biochemical changes were found in 8 (5.2%) patients- clozapine 1 (20%) followed by risperidone 6 (8.9%) and olanzapine 1 (1.61%) group. Remaining 34 cases were observed with 'borderline' lipid changes. In case of clinically significant biochemical changes, overall female preponderance was found. The female: male ratio was All patients 1.67:1, Ris group 2:1, Ola group 1:0 and in Clozapine group 0:1. At the study endpoint, 41 cases were observed with lipid changes (Ris 23, Ola 16, Cloz 2) all with 'borderline' lipid change status that is no patient had 'clinically significant' abnormality in lipid levels.

Thus all the 8 cases with clinically significant lipid changes at week 12, improved at subsequent endpoint biochemical assessment. Of these 8 patients, in 2 patients receiving risperidone having TC 242 3 mg/dL and 244.1 mg/dL respectively, due to their disease symptom improvement, the risperidone dose was reduced to maintenance dosage of 3 mg from 4 mg from week 36 onwards and 2 mg from 4 mg from week 24 onwards during study period respectively in these two cases. In rest of the 6 cases no changes in antipsychotic dose or other drug intervention was done, except in all cases routine-practice advice of...
change in life-style (diet and exercise) was given. These findings also reveal that effect of atypical antipsychotics on lipid changes occur within initial 12 weeks of treatment. This emphasizes the need of adhering to metabolic monitoring schedule of recommended guidelines such as ADA/APA guideline.

The present study findings with respect to lipid changes are consistent with findings of a 12-week observational study by Bamwal et al, 2012 in which regardless of statistically significant changes found in total cholesterol and triglycerides after 12 weeks, they were still within clinically normal range [TC: 159.91 (SD 7.24), TG: 121.67 (SD 10.65)]. However, compared to other studies, the present study findings show comparatively smaller occurrence of clinically significant lipid changes (Strous et al 2006, Murashita M et al 2007, Umadevi and Murugam 2009). Our study participants differ from those in the other studies. Strous et al included both in- and out-patients while the study by Umadevi P. and Murugam S. consisted of in-patients of good socioeconomic background. In contrast, our study population included outpatients of public hospital receiving free medical consultation and treatment including medication suggestive of relatively poor economic background.

The findings of the lipid biochemical parameters in present study at 12 weeks showed that among three groups risperidone was the only drug having effect on total cholesterol and LDL-cholesterol, and in case of triglycerides the clozapine was having higher effect compared to risperidone and olanzapine. The effect of clozapine on triglycerides well corroborates with the findings of previous studies (Henderson DC et al, 2000 and Wirshing DA et al, 2002). The findings related to effect of risperidone on lipids levels differ with findings of studies which reported to have no or modest effect or even decrease in blood lipids levels (Strous et al 2006, Bamwal et al, 2012). In our study in spite of showing increased lipid levels no participant had FBG level >126 mg/dl suggesting no correlation between lipid disturbances and glucose dysregulation.

The overall occurrence of clinically significant biochemical changes over the study period of 48 weeks were found in 8 patients (5.2%) with group bifurcation of clozapine 1(20%), risperidone 6(6.9%) and olanzapine 1(1.61%) among individual group (at 12 week). This is comparatively smaller occurrence compared to other studies focusing metabolic effects (Strous et al 2006, Murashita M et al 2007, Umadevi and Murugam 2009).

Of note, the present study consists of biochemical parameter findings of fasting level. As concluded by Smith RC et al, 2010 in his study, the chronic schizophrenic patients treated for years with first and second generation antipsychotics may develop tolerance to the effects of olanzapine on increasing fasting triglycerides and other lipids, but some underlying metabolic abnormalities may be revealed in postprandial tests of lipid metabolism. So, measurement of postprandial triglycerides and related lipid
levels (provocative tests), in addition to fasting levels may be helpful in identifying metabolic effects of olanzapine and other atypical antipsychotics in chronically treated schizophrenics.

In present study of 8 cases with clinically significant biochemical changes at week 12, except in 2 cases, wherein the 1 mg and 2 mg dose reduction in risperidone was done as part of clinical symptom improvement, in rest of the 6 cases no changes in antipsychotic dose or other drug intervention was done, except as in all cases routine-practice advice of change in life-style (diet and exercise) was given. Henderson and colleagues (2000) noted a significant increase in serum triglycerides in patients treated with clozapine, and that this increase was nonsignificantly associated with the development of diabetes or nonconfirmed diabetes. They also found that total serum cholesterol was not associated with development of diabetes or nonconfirmed diabetes. This also suggests possibility that atypical antipsychotics like clozapine may not be independent risk factors for hyperlipidemia and glucose/insulin dysregulation, but may instead be modifiers of other risk factors, such as family history, obesity, diet, age, etc (Ferraioli et al, 2004)

Treatment-emergent Adverse Effects (TEAEs)

The atypical antipsychotics have differing adverse event profiles, both in short- and long-term. In present study (N=168, safety set), weight gain 53(31.5%) was the most frequent adverse event followed by EPS 26(15.5%). The rest of the adverse events occurred in less than 10% of patients.

(a) Treatment-emergent Extrapyramidal Side Effects (EPS)

Atypical antipsychotics are less likely than typical antipsychotics to cause EPS, in fact, that is how they got the atypical label. Among these agents, the hierarchy of EPS risk is risperidone > olanzapine = ziprasidone = aripiprazole > quetiapine > clozapine (Tandon and Jibson, 2003) Based on D2 receptor binding affinity, Seeman and Tallen (1998) concluded that those antipsychotics such as risperidone that elicit movement disorders bind more tightly to D2 receptors, whereas antipsychotics such as olanzapine and clozapine that elicit few or no movement disorders bind loosely to D2 receptors and dissociate more rapidly (Maguire GA, 2002).

Treatment-emergent extrapyramidal side effects (EPS) are among important measures of assessing tolerability of antipsychotic agents. Rates of patients experiencing EPS and measures of severity of symptoms were not found to be different among the drugs in most trials. Small numbers of studies found worse EPS outcomes with risperidone compared with olanzapine, clozapine, or quetiapine although the specific measures on which risperidone performed worse were not consistent across these studies.
Clozapine and ziprasidone were also found to have worse outcomes than olanzapine on a limited number of outcomes in a few trials (McDonagh et al., 2010).

In a 12-week-long prospective naturalistic observational study comparing risperidone (n=38), olanzapine (n=38) and clozapine (n=55) in inpatients and outpatients, Strous RD et al. (2006) observed that only individuals receiving clozapine indicated improvement in tardive dyskinesia (as expressed in AIMS scores) over the course of the study. No differences were noted between the three subgroups regarding effects on Parkinsonism or akathisia suggesting that all three demonstrate similar effects, or lack thereof, on these ubiquitous adverse effects of antipsychotic medications, commonly observed with typical antipsychotic medications.

In the CATIE Phase I Study, differences were not found between olanzapine, quetiapine, risperidone, or ziprasidone in the incidence of extrapyramidal symptoms identified as an adverse event or akathisia or movement disorders based on rating scales. Similarly, differences were not found between drugs in the subsequent CATIE Phase Ib, Phase IIE, or Phase IIT nor in another trial with multiple drugs (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone). For all other comparisons made in head-to-head trials, at least some differences were found. Of 10 studies of olanzapine and risperidone (2223 patients total) reporting extrapyramidal symptom adverse event data, 8 found no differences between the drugs while 2 (586 patients total) found risperidone to have higher rates or worsening symptoms of extrapyramidal symptoms on measures reflecting akathisia, dyskinesia, dystonia, pseudoparkinsonism, and overall extrapyramidal symptoms. Mean doses of risperidone 5 and 7 mg were compared with olanzapine 13 and 17 mg of olanzapine, respectively. Across these studies, size and quality ratings were similar. One good-quality, short-term trial (N=377) was statistically powered to determine a difference in extrapyramidal adverse event found no differences between the groups on this measure (extrapyramidal adverse event) assessed by Extrapyramidal Symptom Rating Scale (ESRS) scores or use of anticholinergic medications (Conley RR and Mahmoud R, 2001 cited in McDonagh et al., 2010). In this trial the mean dose of olanzapine was below midrange, while the mean dose of risperidone was near the midpoint (5 mg). The other good-quality trial found treatment-emergent and worsening pre-existing extrapyramidal symptoms in 28.9% (N=35) of olanzapine patients and 50.4% (N=61) of risperidone patients (P=0.0006). Dosing in this study also had olanzapine slightly below midrange and risperidone within midrange (Alvarez E et al., 2006 cited in McDonagh et al., 2010).

In the general schizophrenia patient population, clozapine has low risk of EPS across its entire dose range, whereas the incidence of EPS in risperidone and olanzapine is dose related (Juncos J, 2000). In present study, the dosing pattern used in study participants (n=154) - in risperidone group at baseline was 4.39 mg.
In present study, the occurrence of antipsychotic-induced EPS assessed by ESRS scale in three study group patients (N=154) was total 18 (11.7%). Risperidone 9 (10.34%), olanzapine 8 (12.90%) and clozapine 1 (20%) Of these 18 patients, 6 patients each had 2 different types of EPS in each of them and 1 patient was having three different types of EPS. So, total EPS occurrence among these 18 patients was 26. The occurrence of different EPS in three groups was: In risperidone group (in 9 patients) and olanzapine group (in 8 patients): tremors (hands) > increased salivation = slurring of speech were seen. Others like akathisia, tardive dyskinesia, rigidity and pill-rolling movement were seen in 1 to 2 patients In clozapine group, 1 patient (20%) showed increased salivation and slurring of speech There was no statistically significant between-group difference found among three groups as regarding EPS occurrence (p > 0.05). There was no persistence of EPS as assessed by ESRS scale at study endpoint in any of these 18 patients indicating their resolution during study period. In a recent retrospective study of EPS caused by SGAs (olanzapine, risperidone, aripiprazole, quetiapine, and ziprasidone) in 69 patients, there were 13 reports of EPS in 12 patients (18.9%) This is somewhat higher than our data (Lahon K, et al 2012).

The occurrence of EPS in present study should be seen in light of unrestricted usage of central anticholinergic trihexyphenidyl (benzhexol) as concomitant medication due to naturalistic treatment setting. Of 154 analysed patients, use of trihexyphenidyl was- Cloz 4(80%) followed by Ris 64(73.6%) and Ola 23(37.1%) at baseline, and Ris 72(82.8%) followed by Cloz 4(80%) and Ola 26(41.93%) patients at endpoint The prophylactic usage of anticholinergic agent, trihexyphenidyl is a routine clinical practice in the present clinical setting. This can possibly explain no significant difference in EPS between the three groups. However, while masking of EPS can be achieved with prophylactic anticholinergic treatment, the risk of tardive dykinesia is not reduced, but rather potentially increased, and recent data suggest that anticholinergic medication load is associated with decreased efficacy of cognitive remediation treatment (Kane JM et al., 2010).

(b) Other Treatment-emergent Adverse Effects

As reported in a detailed review on atypical antipsychotics by Conley RR et al, 2005 EPS, most notably akathisia, sexual dysfunction and weight gain, are the three most often cited adverse effects associated with nonadherence. Spontaneously reported AEs with risperidone are insomnia (26%), agitation (22%),
rhinitis (10%) and GI complaints such as vomiting, dyspepsia, nausea, constipation and abdominal pain in about 4-7% of patients. Because of risperidone’s alpha blocking activity, orthostatic hypotension is generally seen during the initial dose titration and is usually transient. The most frequently reported AEs with olanzapine in clinical trials are somnolence (26%) and agitation (23%). Insomnia in 20%, hypotension (5-7%) and anticholinergic effects such as constipation, dry mouth and tachycardia occur in 7-9% (may be more frequent at higher doses) of patients. Transient increases may be seen in alanine transferase (ALT, SGPT) but usually normalize with olanzapine continuation. In placebo-controlled studies, alanine transferase (ALT, SGPT) elevations of >3 times the ULN range were observed in 2% of patients. Among most frequently occurring spontaneously reported AEs from clinical trials with clozapine are drowsiness/sedation (39%) and salivation (31%). Other frequently occurring side effects reported in trials with clozapine include tachycardia (25%), dizziness (19%) and constipation (14%), excessive sweating (6%), orthostatic hypotension often self-limiting that occurs transiently during clozapine initiation and titration (6%), clozapine-associated cardiomyopathy and cardiorespiratory arrest, urinary incontinence occurs (in about 1%), the dose-related risk of seizures (1% to 2% at doses less than 300 mg/day, similar to traditional antipsychotics and approximately 5% at doses greater than 600 mg/day), and lastly agranulocytosis (0.8%), although the risk decreases after the first six months.

In present study, 42 different types of treatment-emergent adverse events of varying severity were observed. Incidence of common treatment-emergent adverse effects with > 2% occurrence (total and in individual drug) were in the following order: weight gain followed by EPS, decrease in HDL, insomnia, sedation, giddiness, weight loss, increase in total cholesterol, headache, general weakness. Except for the weight gain (31.5%) and extrapyramidal side effects (15-50%), rest of the AEs occurred in less than 10% of patients. Some AEs like sedation/drowsiness have been reported to be more frequent in previous studies like a 52-week randomized study by McEvoy et al (2007) reporting drowsiness in 50% or greater in patients on olanzapine, quetiapine or risperidone therapy. However sedation/drowsiness was found to be less frequent in the present study - 20% in clozapine > 7.5% in risperidone > 4% olanzapine groups. Insomnia also has been reported with risperidone in 26% (Conley 2005) compared to 7.7% in our study, maximum (10.6%) in risperidone, 4.4% in olanzapine, and none in clozapine group. Tollefson (2001) reported hypersalivation 2 (2.2%) in olanzapine and 26 (28.9%) in clozapine patients. Dry mouth, constipation, tachycardia are among the anticholinergic adverse effects (related to m1 muscarinic receptors) of antipsychotics and anticholinergic medication like trihexyphenidyl (benzhexol) given as concomitant medication. Olanzapine and clozapine have higher relative affinity for m1 muscarinic receptors compared to risperidone which has minimal or no affinity for m1 muscarinic receptors (Miyamoto S et al, 2005). Sialorrhoea (or hypersalivation or drooling) with clozapine is a paradoxical response since it has a complex
receptor affinity. Clozapine has marked anticholinergic properties and has been suggested that the balance of its opposing effects on M₃ and M₄ receptors (in salivary glands) may mediate hypersalivation since it is known to exert a full-agonist effect at M₄ receptors; whereas, its affinity for M₃ receptors is lower. Therefore, it is possible that the effects of M₄ receptor stimulation would exceed those of M₃ receptor blockade, resulting in hypersalivation. Another proposed mechanism of clozapine-induced sialorrhea is through its blocking actions at α₂ adrenoceptors. (Cree A et al, 2001; Riverview Hospital, May 2003) In present study, the sialorrhoea was seen in 4(2.4%) patients (N=168, safety set) comprising 2(2.12%) in risperidone, 1(1.45%) in olanzapine and 1(20%) in clozapine patients. The concurrent use of anticholinergic should be taken into consideration while considering the extrapyramidal and anticholinergic side effects in present observational study with naturalistic treatment-setting. This can possibly explain no significant difference in EPS between the three groups.

In present study, of the three female patients receiving risperidone with complaint of menstrual disturbance were investigated for serum prolactin level. Of these three, one patient was found to have prolactin level - 37.7 ng/ml, higher than laboratory defined normal range (1.2 to 19.5 ng/ml), but since in this patient the menstrual cycle resumed and remained asymptomatic, and she was in remission period as far as symptoms of schizophrenia, it was clinician’s decision to continue risperidone at the dose of 4 mg/day. In a 12 week-long prospective naturalistic observational study by Strous RD et al (2006) comparing risperidone (n=38), olanzapine (n=38) and clozapine (n=55) in in- and out-patients, males showed a decreased sexual performance irrespective of the medication. There was no spontaneous reporting of sexual dysfunction in any of three drug groups in present study. On the other hand no case of menstrual disturbance was reported in study by Strous RD et al (2006). Our finding of prolactin disturbance in a female patient receiving risperidone is consistent with higher potential of risperidone in this respect compared to other antipsychotics. Carlson HE (2007) has pointed out the relative potency of prolactin-elevating potential of antipsychotic agents based on D₂ receptor affinity with the relative potency: Risperidone > Paliperidone > Haloperidol > Olanzapine > Ziprasidone > Quetiapine > Clozapine > Aripiprazole. Of note, in a 4-week nonrandomized open-label observational study, Westheide J et al (2008) in 102 in-patients with schizophrenia examined the sexual functioning, subjective well-being, endocrinological parameters as well as psychopathological characteristics. It was reported by Westheide J et al (2008) that increased prolactin levels do not seem to be decisive for antipsychotic induced sexual dysfunction.
In present study, AEs in three drug groups (safety set, N=168) were assessed in addition to occurrence, for severity as well as WHO causality grades. Most AEs were of mild to moderate severity. No serious adverse event was observed in this study. Moreover, no treatment discontinuation due to AEs was observed in any patients. The WHO Causality Grades of adverse effects assessed among three groups with respect to safety set (N=168) were as follows: Risperidone Possible 93 (55.35%), Unlikely 32 (19%), Probable 26 (15.47%), Unclassified 1 (0.6%); Olanzapine Possible 88 (52.38%), Unlikely 13 (7.74%), Probable 8 (4.76%), Clozapine: Possible 07 (04.16%), Probable (1.78%)

Of note, the incidence of AEs observed in present study should be seen considering the fact that since it was an observational study with naturalistic treatment setting, there was no restriction on dosage in case of study drugs and for using concomitant medication. In present study the usage at baseline of benzodiazepines was 130(84.4%) and of trihexyphenidyl (benzhexol) 91(59%). Only 3(1.8%) patients received mood stabilizers during present study. In 1 patient on risperidone (0.65%), sodium valproate was used from baseline to endpoint. No change in weight and BMI, and no biochemical abnormalities were observed in this patient. In another patient in risperidone group (0.65%), lithium carbonate was prescribed during third visit (week 8), however this patient was lost-to-follow up from subsequent visit. In 1 patient with olanzapine (0.65%), lithium carbonate was prescribed during second visit (week 4), but was discontinued from subsequent visit.

**Effectiveness of Atypical Antipsychotics Measured by Time-to-Medication (Treatment) Discontinuation**

Time to all-cause medication discontinuation (for all or any cause) has been recognized as an important global index of antipsychotic effectiveness. It is considered a composite proxy measure of treatment efficacy, safety, and tolerability. It is a clinically meaningful outcome measure that integrates patients’ and clinicians’ judgments of efficacy, safety, and tolerability into a global measure of effectiveness that reflects their evaluation of therapeutic benefits in relation to undesirable effects (Lieberman J A, et al., 2005). Time to treatment discontinuation is increasingly used as a primary outcome measure in antipsychotic effectiveness research (Shajahan P et al., 2010).

Longer time to discontinuation of antipsychotic medication for any cause has been shown to be associated with greater symptom improvements in the treatment of schizophrenia (Dunayevich, 2007). Persistence refers to the duration of time a patient continues to take a prescribed drug. In the setting of a study, this may also be referred to as early discontinuation or withdrawal from treatment during the study period and can be assessed as a rate or the time to discontinuation. The reasons for discontinuing the assigned drug treatment encompass inadequate efficacy as well as intolerable side effects, time-to medication (treatment) discontinuation is considered a good measure of overall effectiveness. This global proxy
measure of medication effectiveness was also the primary outcome measure in the National Institute of Mental Health–CATIE (The Clinical Antipsychotic Trials of Intervention Effectiveness) project (Ascher-Svanum H et al, 2006, McDonagh et al., 2010).

In the present study, of 154 patients analyzed, 30 patients (19.5%) discontinued during study before 48 weeks due to all-cause (or any cause). Group-wise discontinuation for various reasons was in the following order: due to all-cause (or any cause) Risperidone 18 (20.6%) > Olanzapine 12 (19.3%) > Clozapine 0(0%) patients; due to therapeutic inefficacy (clinician’s judgement): Risperidone 4(6.6%) > Olanzapine 1(1.6%) > Clozapine 0(0%) patients; due to lost-to-follow-up (reason unknown): Risperidone 13 (14.9%) > Olanzapine 9(14.5%) > Clozapine 0(0%) patients, due to patient’s uncooperative (clinician’s judgement). Olanzapine 2(3.2%) > Risperidone 1(1.1%) > Clozapine 0(0%) patients. However, no patient discontinued due to intolerable adverse effects in this study. This finding of no discontinuation due to intolerable adverse effects is different from previous comparative studies with respect to the causes for discontinuation of antipsychotics reporting intolerable adverse effects as one of the important cause for noncompliance. In CATIE trial, Lieberman JA et al (2005) reported 34(10%) and 62(19%) discontinuation due to intolerability for risperidone and olanzapine respectively. In another report of CATIE trial by Stroup TS et al(2006), 7(10%) and 13(20%) discontinuation due to intolerability was reported for risperidone and olanzapine respectively.

In present study, in treatment discontinuation rate due to all (or any) cause, there was no statistically significant difference found between the three groups (p > 0.05). In a 52-week randomized, double-blind, flexible-dose, multicenter study which evaluated the overall effectiveness (as measured by treatment discontinuation rates) of olanzapine, quetiapine, and risperidone in 400 patients early in the course of psychotic illness, olanzapine, quetiapine, and risperidone demonstrated comparable effectiveness as indicated by similar rates of all-cause treatment discontinuation (McEvoy JM et al, 2007). The findings of the comparable effectiveness of olanzapine and risperidone in present study assessed by treatment discontinuation rate are in line with the findings reported by McEvoy JM et al, 2007.

Treatment or medication discontinuation rates are higher among patients with schizophrenia than in other diseases. In Schizophrenia Outpatient Health Outcomes (SOHO) study, a 3-year prospective, observational, longitudinal study on the effectiveness of antipsychotic treatment for schizophrenia in the outpatient setting (Haro JM et al, 2003a-cited by Haro JM et al, 2006), which provided an excellent opportunity to analyze treatment discontinuation in routine clinical practice, rates of antipsychotic treatment maintenance were much higher than the findings of the CATIE trial, phase I (Lieberman JA et al, 2005). While 64% to 82% of patients in the CATIE study discontinued their medication before 18 months of treatment, in the SOHO...
study, the figures for 18 months were between 28% and 55%, depending on the medication prescribed at baseline. Both studies were highly consistent in the finding that olanzapine showed the highest rates of medication maintenance, although differences among other antipsychotics were found. Medication discontinuation for any cause for clozapine, olanzapine and risperidone before 36 months were 33.8%, 36.5% and 42.7% patients and the duration was 15, 15 and 9 months respectively (Haro JM et al, 2006). Thus the findings of present study are consistent with regard to discontinuation rates in the same order.

In one of the most cited multicenter double-blind CATIE study (phase I) on the effectiveness of antipsychotic drugs (Lieberman J.A, et al, 2005), the time to the discontinuation of treatment for (all or any cause was significantly longer in the olanzapine group than in the quetiapine (P < 0.001) or risperidone (P = 0.002) group compared to perphenazine (P = 0.021) or ziprasidone (P = 0.028) group. Whereas the times to discontinuation because of side effects were similar among the groups, the rates differed (P = 0.04), olanzapine was associated with more discontinuation for weight gain or metabolic effects, and perphenazine was associated with more discontinuation for EPS (cited in Raja M, 2009). In CATIE study (phase 2E) time to discontinuation was found longer with clozapine (10.5 months) than olanzapine (2.7 months, P=0.12), immediate-release quetiapine (3.3 months, P=0.01), or risperidone (2.8 months, P<0.02). Further analysis of the time to discontinuation due to lack of efficacy indicated that clozapine was superior to all 3 of the other drugs. In CATIE study (phase 2T) time to discontinuation was statistically significantly longer with risperidone (7 months) and olanzapine (6.3 months) than with quetiapine (4 months) or ziprasidone (2.8 months), but no difference was found between risperidone and olanzapine (hazard ratio 1.02, 95% CI 0.67-1.55). Twelve retrospective observational studies have reported time to discontinuation with comparisons of atypical antipsychotics. The mean time to discontinuation with olanzapine compared with risperidone was significantly longer with olanzapine in 7 studies (mean 251 days for olanzapine and 173 days for risperidone), while differences were not found in 3 studies (mean of 235 days to discontinuation for olanzapine and 228 for risperidone). Pooling of these results indicated a statistically significant difference of up to 66 days (95% CI, 59 to 73) longer with olanzapine. Removal of a single study with much longer duration of treatment than the others indicated a smaller, but statistically significant, difference of 46 days (95% CI, 43 to 49) (McDonagh et al., 2010).
In present study out of 154 participants, the mean survival time (time until medication or treatment discontinuation before 48 weeks) was 48.00 ± SD 00.00 weeks with no discontinuation in clozapine group followed by risperidone 41.79 ± SD 13.34 weeks and olanzapine 40.71 ± SD 15.30 weeks. Although no statistically significant difference was found between three groups in this respect (p > 0.05), 7 to 8 weeks mean difference in survival time (time until medication or treatment discontinuation before 48 weeks) in clozapine group compared to risperidone and olanzapine may have clinical relevance in terms of treatment effectiveness. Thus overall effectiveness of clozapine, olanzapine and risperidone based on time-to-treatment discontinuation in present study was found comparable. Although these findings of the study should be interpreted taking into account the small sample size in clozapine group (n=5) compared to other two groups, they corroborate with the available evidence which indicates that no other antipsychotic drug (neither of first nor of second generation) has shown superior clinical effectiveness in the treatment of psychotic disorders, with the significant exception of clozapine (Raja M, 2009).

Correlations of QOL with GAF and PANSS

Correlations of Patient-rated disease-specific Subjective Wellbeing assessed by Subjective Well-being under Neuroleptic treatment (SWN-20) scale and positive and negative domains of its five sub-scales with Clinician-rated Psychopathology (PANSS total and three sub-scales) and Global Functioning (GAF scale) at baseline and endpoint were assessed by Spearman’s Rank Correlation Coefficient (rho). With few exceptions, in most of the cases there was moderate to strong positive correlation between patient-rated SWN-20 (and its subdomains) and Global functioning (GAF) assessed by clinicians. However, as far as correlation between SWN-20 and PANSS scores is concerned it was found that, except SWN-mental functioning and physical functioning positive and negative scores, rest of the statistically significant correlations between SWN-20 and its subdomains and PANSS and its subdomains were having moderate to very strong, negative or inverse correlation. It shows that the assessment of patient-rated SWN-20 and of clinician-rated PANSS are not strongly related. This indicates that the assessment of subjective well-being under antipsychotic treatment made by patients and assessment of psychopathology made by clinicians differ. This is in accordance with the findings of a double-blind clinical trial of olanzapine and clozapine that the total SWN score, as well as the subscales were only moderately correlated with the PANSS scores indicating that patients and psychiatrists perceive treatment differently (Naber et al 2005).

The limitations of the present study are 1) Only schizophrenic outpatients on antipsychotic monotherapy given orally were included. This means that the patients with the more disease severity were not included. 2) This was an observational study with open-label design, which can bias the effectiveness findings. Since the patients were not randomized to treatment, there could be unobserved differences between the treatment groups that may confound the study results. 3) Small sample power in clozapine group. Clozapine by itself is considered reserved in treatment-resistant cases. However, this also should be seen in
Discussion

light of present study design being observational with naturalistic treatment setting. In present clinical setting, the clozapine’s prescription trend is more often to be as an add-on therapy in patients with inadequate therapeutic response to other antipsychotics rather than as monotherapy. 4) Although, waist circumference is an important measure to be considered for metabolic evaluation, this was not feasible owing to ethical reasons in female patients due to lack of availability of female staff to carry the same throughout the study period. 5) Not examining the effect of atypical antipsychotics in patients having cardiometabolic comorbidity requiring detailed investigation profile due to financial constraints. 6) Not examining the role of risk factors such as ethnicity, family history or exercise.

The strengths of the present study are 48-weeks long observation period and the disease diagnosis based on DSM IV criteria and inclusion of subjective well-being as a component of quality of life as one of the outcomes of drug therapy. The observational design with naturalistic treatment setting represents the real-world routine clinical practice.

To conclude this prospective observational 48-week study of three antipsychotics—risperidone, olanzapine and clozapine in outpatients of schizophrenia shows no remarkable differences between them in terms of efficacy, tolerability and overall effectiveness. Findings of present study also reveal the effect of atypical antipsychotics on lipid changes within initial 12 weeks of treatment. Looking to the observational nature and its sample profile, present study findings can not be generalized to all Indian patients. However, it upholds the periodic metabolic monitoring based on recommended guidelines such as ADA/APA guideline along with role of education, diet control and simple behavioural measures in averting metabolic abnormalities in patients with schizophrenia on long-term treatment with atypical antipsychotics. More such long term studies are necessary in different therapeutic settings including inpatients, patients with comorbidities like diabetes and also involving different groups of patients in terms of socioeconomic class.