CHAPTER 6

SUMMARY AND CONCLUSIONS
The present study was conducted with an aim to examine effectiveness, subjective well-being and tolerability (with focus on metabolic effects) of three atypical antipsychotics in schizophrenic patients. This prospective, observational study was conducted in out-patients diagnosed with schizophrenia (DSM-IV criteria) and undergoing antipsychotic treatment on the best possible clinical knowledge, judgement and experience of the attending psychiatrist(s), out of whom those patients prescribed monotherapy with risperidone or olanzapine or clozapine in routine clinical practice with naturalistic treatment setting (without restriction on dosage or concomitant medications) and agreeable for the biochemical (fasting blood glucose and lipid profile) tests were selected for 48-week observational follow-up.

The study participants were observed for the following visits- baseline, week 4, week 8, week 12, week 16, week 20, week 24, week 30, week 36, week 42 and week 48 (endpoint). In three treatment groups, at every visit the parameters observed were study drug treatment, concomitant drug treatment, weight, treatment-emergent adverse events, extrapyramidal side effects (as assessed by ESRS scale), subjective well-being (a patient rated disease-related QOL measure by SWN-20 scale), global functioning (by GAF scale), patient’s psychopathological symptoms (by PANSS scale), illness severity (by CGI-S scale) and illness improvement (by CGI-I scale measured at all visits except baseline). Pulse, B.P., and weight were observed at baseline, week 4, week 8, week 12, week 24, week 36, and week 48 (endpoint). Fasting blood sugar and lipid profile were measured at baseline, week 12 and week 48 (endpoint). Urine pregnancy test was done in females of child-bearing age at baseline, week 12, week 24, and week 48 (endpoint). In case of clozapine group, periodic complete blood count was done as per clozapine drug’s defined requirement, and ECG was done at baseline and at endpoint. Relevant tests were done if required and directed by psychiatrist as and when needed.

Of 182 out-patients with schizophrenia (DSM-IV criteria) receiving atypical antipsychotic monotherapy (risperidone or olanzapine or clozapine), 14 patients not fulfilling selection criteria were excluded and 168 out-patients were enrolled. Out of 168 participants enrolled, 154 were analyzable at the end of the study consisting of risperidone (n=87), olanzapine (n=62) and clozapine (n=5). The results were analysed using appropriate statistical tests to evaluate and compare the effectiveness and tolerability of the three drugs- risperidone, olanzapine and clozapine in patients with schizophrenia.
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Of 154 study participants analysed, with all the three drug groups was found a progressive improvement in patients' overall functioning and subjective wellbeing based on mean global assessment of functioning (GAF) score and mean subjective wellbeing scores-(SWN-20—total score and positive and negative domains of five SWN-20 subscales viz mental functioning, self control, emotional regulation, physical functioning and social integration except in case of mental functioning positive domain in clozapine group over 48-weeks study period Similarly all the three drug groups also exhibited improvement in clinical psychopathological symptoms and severity of illness as measured by progressive decrease in mean PANNS total score, mean PANNS Positive score, mean PANNS negative score, mean PANNS general Psychopathology Score, and progressive decrease in mean CGI severity score Higher PANSS response rate was observed for clozapine and olanzapine compared with risperidone. However, there was no significant difference in percentage (%) change in PANSS total score at endpoint compared to baseline (p > 0.05). There was also overall illness improvement based on CGI improvement score at endpoint over the period of 48 weeks in all the three groups with mean changes in clozapine (1.8) followed by olanzapine (1.27) and risperidone (1.22) with no significant difference between three groups (p > 0.05). Thus three drug groups were found to have comparative improvement at endpoint over the period of 48 weeks irrespective of baseline psychopathological scores.

Of 154 study participants analysed, mean weight gain was higher in olanzapine group followed by clozapine and modest weight gain with risperidone The mean BMI changes were consistent with changes in mean weight gain and found to be higher in olanzapine group followed by clozapine and risperidone 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, clozapine group does not differ from olanzapine and risperidone groups in weight gain and BMI at endpoint. Over a study period of 48 weeks, clinically significant weight gain (≥ 7% increase from baseline) at endpoint was found to be higher in olanzapine group in 26(42.0%) patients followed by clozapine 1(20.0%) and risperidone 15(17.24%) groups. Of these 42(27.3%) patients with ≥ 7% weight gain, there was preponderance in patients with normal BMI- 24 and obese- 9 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. 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
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antipsychotic medication along with underlying predisposition to significant weight gain over time may need consideration

In respect of fasting blood glucose (FBG), there was significant difference between risperidone and clozapine groups ($p=0.041$), and between olanzapine and clozapine groups ($p=0.011$) at the endpoint. However, no significant within-group difference was found at week 12 and endpoint data compared to baseline in any of the three groups ($p > 0.05$). There were no cases with 'high' (clinically significant) FBG changes ($\geq 126$ 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 all three drug groups.

In respect of changes in lipid parameters among three groups, with respect to TC, TG, LDL-C and HDL-C, no significant between-group difference was found among three groups at BL or EP; no within-group significant difference was found in three groups between BL and W12 or between BL and EP except in case of TC ($p < 0.01$) and LDL-C ($p = 0.001$) in risperidone group between BL and W12. Clinically significant post baseline changes in fasting lipids (TC $\geq 240$ mg/dL, TG $\geq 200$ mg/dL and LDL-C $\geq 160$ mg/dL) at week 12 were noted in 8(5.2%) patients with group bifurcation of clozapine 1(20%) followed by risperidone 6(6.9%) and olanzapine 1(1.61%). Risperidone was the only drug found to have effect on TC 5(5.75%) and LDL-cholesterol 3(3.45%) patients, and in case of triglycerides clozapine to have effect on 1(20%) followed by risperidone 2(2.3%) and olanzapine 1(1.61%) patients at 12 week. However, all the cases with clinically significant lipid changes at week 12, improved with no clinically significant biochemical changes during subsequent endpoint biochemical assessment. Of these 8 patients, in 2 patients receiving risperidone, due to their disease symptom improvement, the risperidone dose was reduced during study period. In rest of the 6 cases no change in antipsychotic dose or other drug intervention was done. In all the cases routine advice of change in life-style (diet and exercise) was given.

Tolerability profile of three drug groups (safety set, N=168) revealed that weight gain was the most common adverse effect in 53(31.5%) patients followed by extrapyramidal side effects 26(15.5 %), reduction in HDL cholesterol 15(8.9%), insomnia 13(7.7%), sedation 11(6.5%), giddiness 9(5.35%), weight loss 5(3.0%), increased total cholesterol 5(3%), increased triglycerides 4(2.4%) = headache 4(2.4%) = general weakness 4(2.4%). Except for the weight gain (31.5%) and extrapyramidal side effects (15.50%), rest of the AEs occurred in less than 10 % of patients. None of the adverse effects were serious. Among three drug groups, weight gain was most frequent adverse effect with
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Olanzapine 29 (42.03%) patients followed by clozapine 2 (40.00%) patients and risperidone 22 (23.40%) patients.

The occurrence of antipsychotic-induced extrapyramidal side effects (EPS) assessed by ESRS scale in three study groups (N=154) was: total 18 (11.7%) patients, most frequent with clozapine 1 (20%) followed by olanzapine 8 (12.90%) and risperidone 9 (10.34%). Of these 18 patients, 6 patients 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. There was no statistically significant between-group difference found as regarding EPS occurrence (p > 0.05). There was no persistence of EPS assessed by ESRS scale at study endpoint in any of these 18 patients indicating their resolution during study period. The occurrence of EPS in present study should be seen in light of unrestricted usage of concomitant medication due to naturalistic treatment setting. Next to benzodiazepines, anticholinergic trihexyphenidyl (benzhexol) was maximally prescribed comedication found both at baseline [91 (59%)] and at endpoint [102 (66.2%)] 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%) 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.

Time-to-discontinuation of treatment (for all or any cause) is recognized as an important global index and a broad proxy measure of overall antipsychotic treatment effectiveness that integrates patients’ and clinicians’ judgments of efficacy, safety and tolerability. Out of 154 study participants, the discontinuation rate with respect to discontinuation due to all-cause (or any cause), there was no discontinuation in clozapine group followed by 12 (19.3%) patients in olanzapine group and 18 (20.6%) patients in risperidone group. However, there was no significant difference among three groups (p > 0.05). The mean survival time (time until medication discontinuation before 48 weeks) was found 48.00 ± 00.00 weeks for clozapine group with no discontinuation followed by risperidone 41.79 ± 13.34 weeks and olanzapine 40.71 ± 15.30 weeks with no significant difference between three groups in this respect (p > 0.05) although 7 to 8 weeks mean difference in survival time 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 treatment discontinuation rate and time-to-treatment discontinuation in present study was found comparable.
In case of complex correlation dynamics 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. As far as correlation dynamics between patient-rated SWN-20 and clinician-rated PANSS scores, except in case of 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. This indicates that the assessment of subjective well-being under antipsychotic treatment made by patients and assessment of psychopathology made by clinicians differ.

In summary, results of this 48-week prospective, observational study with naturalistic treatment setting in outpatients of schizophrenia of three antipsychotics- risperidone, olanzapine and clozapine 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. 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. Since atypical antipsychotics differ in their adverse effect profile, the regular baseline screening and follow-up monitoring can also help in individualizing the selection of atypical antipsychotic suitable to cardiometabolic profile of the concerned patient while prescribing it for the first time or while taking decision for addition or switching to another atypical antipsychotic. Further double-blind prospective studies in Indian outpatients with schizophrenia with wide socioeconomic background undergoing long-term atypical antipsychotic treatment are required in order to confirm findings of such observational studies.