CHAPTER 3

MATERIALS AND METHODS
3.0 MATERIALS AND METHODS

3.1. Study Design
This was a prospective observational study in which no therapeutic intervention was recommended, but was left on the best possible clinical knowledge, judgement and experience of the attending clinician(s). The study was carried out at the psychiatric out-patient department of the public hospital, mental health hospital, Ahmedabad.

3.2. Selection of Patients: (study population)
Those outpatients diagnosed with schizophrenia and were prescribed any one of the atypical antipsychotic monotherapy (risperidone or olanzapine or clozapine), and those suitable as per following inclusion-exclusion criteria, were selected.

Inclusion Criteria:

- Outpatients of 18-65 years age, male or female, diagnosed with Schizophrenia and who meet DSM-IV diagnosis criteria of the disease.
- Patients having total score of ≥ 60 on the total PANSS at the time of screening.
- Patients diagnosed with schizophrenia and who need to initiate risperidone or olanzapine or clozapine, OR who need switch from other antipsychotic(s) to risperidone or olanzapine or clozapine, OR who are being currently prescribed antipsychotics like risperidone or olanzapine or clozapine based on clinical criteria as judged by attending psychiatrist.
- Patients in good physical health and not suffering from any medical disorder that might mimic psychosis.
- Patients with medical illness and/or concomitant medications (e.g., hypoglycemic, antihypertensive or other such agents) and having at least last 3 months of stable clinical condition as judged by treating psychiatrist and/or with laboratory abnormalities ± 20% of the upper limit of laboratory reference values of - fasting blood glucose (110 mg/dL), and of fasting lipids - total cholesterol (240 mg/dL), triglycerides (165 mg/dL), LDL cholesterol (165 mg/dL) and - 20% of the lower limit of laboratory reference values of HDL cholesterol (35 mg/dL) or judged clinically insignificant by treating psychiatrist.
- Patient (and/or his/her authorized legal representative, if appropriate) agreeable and cooperative to visit the hospital clinic for clinical, psychiatric and psychometric assessments, biochemical (fasting...
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blood glucose and lipid profile) laboratory tests and other tests as may be required by the attending psychiatrist in the routine clinical practice during the 48 weeks observation period.

- Patient (and/or his/her authorized legal representative, if appropriate) agreeable and cooperative to visit the hospital clinic for the assessment of subjective well-being under antipsychotic treatment during the 48 weeks observation period

Exclusion Criteria:

- Major medical co-morbidity (e.g. pulmonary, cardiac, hepatic, gastrointestinal, endocrine and renal) as judged by treating psychiatrist
- Women currently breast-feeding or pregnant or of child bearing age unwilling to use barrier contraceptives or who is considering pregnancy within 48 weeks observational period
- Significant risk of suicidal or homicidal behaviour reported by treating psychiatrist within last 4 weeks
- Participation in another clinical trial within 4 weeks prior to enrolment into this study.
- Current use of alcohol or substance dependence other than caffeine and tobacco.
- Use of depot antipsychotic/electroconvulsive therapy within 6 weeks prior to screening
- Patients taking concomitant medication (e.g. weight-reducing, hypolipemic or other such agents) that may confound the study outcomes

Sample Size:

Based on study design and duration, study population (patients diagnosed with schizophrenia who meet DSM-IV diagnosis criteria of a disease and having total score of ≥ 60 on the total PANSS at the time of screening), any one of the three study medications prescribed as monotherapy and other Inclusion and Exclusion criteria of the study, the sample size was worked out using sample size calculator (MaCorr Research, 2003) to be 93 patients, rounded off as 95 patients considering confidence level (C.L.) of 90% and confidence interval (C.I.) of 5%. Considering the dropout rate of 15%, the sample size was worked out to be 109 and finally rounded off as 111 patients

3.3. Study End Points:

Primary Outcome Measures

- Assessment of functioning and subjective wellbeing of patients receiving any of the three antipsychotics.
- Assessment of the tolerability (with focus on metabolic effects) of individual study antipsychotic.
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Secondary Outcome Measures.
- Assessment of efficacy of study antipsychotic in improving psychopathology of schizophrenia during the study
- Time to all-cause medication discontinuation: It was the time until medication discontinuation of study antipsychotics (risperidone or olanzapine or clozapine as monotherapy) in enrolled patients with schizophrenia for any and specific cause.

3.4. Study Conduct

- This was a prospective, observational study without any treatment-regimen intervention by the investigator which allowed the clinicians to treat and follow up the patients as in a routine clinical practice.
- After physical examination and psychiatric evaluation, the investigator considered those schizophrenic patients who were already diagnosed for schizophrenia (DSM IV criteria) and who were found to be suitable as per study selection criteria and for monotherapy treatment, and who required either initiation or switch with risperidone or olanzapine or clozapine as monotherapy or who were already prescribed risperidone or olanzapine or clozapine as monotherapy based on clinical knowledge and judgement of the attending psychiatrist and who were agreeable for necessary clinical, psychiatric and psychometric assessments and investigations (including biochemical laboratory tests) as and when required and advised by attending psychiatrist at the beginning and subsequent follow-up visits of the 48-weeks observational period.
- At the baseline of the study, demographic data and baseline characteristics for all the study participants were recorded. Verification of inclusion/exclusion criteria for the purpose of observational study were done.
- Thus among above participants qualified based on verification of inclusion criteria in this study, patients were defined/selected according to antipsychotics prescribed to them by psychiatrists and thus fell in to any one of the three monotherapy treatment groups: risperidone group or olanzapine group or clozapine group.

Dosage Regimen:
In present study, in view of no therapeutic intervention, no specific dosage regimen was recommended. So, individualized flexible dose for both the initial and maintenance therapy during the course of study was prescribed by attending psychiatrist(s) based on his/her clinical judgement and experience so as to facilitate optimization and tolerability in case of the individual study participant.
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- **Protocol Violation:**
  In the present study, in view of no therapeutic intervention, no specific protocol violations were defined, however, basic withdrawals and dropouts criteria were defined as follows, only for the purpose of ethical considerations and study outcomes evaluation at the end of the study.

**Withdrawal Criteria**
A patient to be withdrawn from the study if
- The Investigator believes it is in the best interest of the patient to be withdrawn
- The patient (or the patient’s legally authorized representative) withdraws consent for participation in the study.
- A female patient becoming pregnant.

**Dropouts**
A patient was considered as dropout from the study if he/she discontinued due to any reason or lost to > 3 (three) consecutive scheduled visits of the study. Both in cases of consent withdrawal and dropout due to any reason, every attempt was made to contact the study participant or his authorized representative. Patients were informed/explained of the benefits of continuing the antipsychotic treatment or with the prescribed antipsychotic medication, even if they do not continue with the study. For the psychiatric, medical and laboratory check-up scheduled at the end point of the study, attempts were made to carry them out after withdrawal from the study in such cases.

**Concomitant and Rescue Medications**
In present study, keeping in view of no therapeutic intervention, no concomitant and rescue medications were defined and were left on clinical judgement of the attending psychiatrist(s). However, for the purpose of ethical considerations and study outcome (end points) data evaluation at the end of the study, it should be mentioned here that if additional antipsychotic was required and given on continual therapeutic basis as best clinically judged by treating psychiatrist in the patient’s benefit, it was considered as relapse and study discontinuation in case of such participant. At the same time, whenever adjunctive or concomitant medications were prescribed, their generic name, dose, and indication were recorded on the appropriate case report forms. In case of requirement of adding/treating the patient with depot antipsychotic or electroconvulsive therapy (ECT) or need for hospitalization, it was considered as relapse and study discontinuation in case of such participant.

Patients’ well being was the attending psychiatrist’s responsibility and he/she would provide all necessary supportive medication, treatment and measures as were required to manage the treatment-emergent adverse effects, serious adverse effects (SAEs) or overdose toxicity. All such measures were recorded in the CRF.
Safety Observations and Evaluations

Safety evaluations during study included documentation of the adverse events, vital signs and laboratory tests as per scheduled assessment and advised by attending psychiatrist. Adverse events during the study were documented at baseline and thereafter during the scheduled visits if they experienced any problems or symptoms since the previous visit. Investigator graded the intensity of events and assessed their causal relationship to the study group medication. Any ± 5 % ‘weight change’ at scheduled assessment visit compared to baseline visit was documented as an adverse event. In case of fasting laboratory biochemical investigations (blood sugar and lipids-cholesterol, triglycerides, LDL cholesterol & HDL cholesterol) done at scheduled assessment visits, any worsening compared to their baseline values were documented as an adverse event. Any additional investigations as and when directed during study by psychiatrist, if carried out, were documented appropriately. The occurrence of parkinsonism, akathisia and dyskinesia were evaluated using appropriate scale.

The study participants having clinical treatment-emergent adverse effects at the last study visit were followed for up to 2 weeks after study completion to assess, and in case of serious adverse effects the follow-up were done maximum up to 4 weeks. In case of worsening of disease or extrapyramidal side effects occurring between two scheduled visits (unscheduled visit), the adverse event was documented at the time of the visit, whereas any other type of adverse event was documented at the scheduled visit. In case of laboratory biochemical abnormalities at the last study visit of the participant, including fasting blood glucose and lipids, no further follow up was done.

The reporting of adverse events (AEs including biochemical abnormalities) was done as specified under the heading given below ‘Reporting of Adverse Events (AE)’. 

Reporting of Adverse Events (AE)

Any serious (fatal or life threatening) and unexpected adverse event, if any was required to be notified within 24 hours after its occurrence to the institutional ethics committee using phone or fax. All other serious AEs, not fatal or life threatening, were required to be reported not later than 14 days to the institutional ethics committee.

Definitions


  Any untoward medical occurrence, including dosing errors, that may arise during administration of study agent, and which may or may not have a causal relationship with the study agent.
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• **Adverse (Drug) Reaction (ADR)** [Farcas and Bojita, 2009]

  A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

  An adverse drug reaction, contrary to an adverse event, is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or reviewing health professional.

• **Unexpected Adverse Event (Experience)**: [ICTDR Investigator Manual, 2003]

  Any adverse experience that has not been previously observed (i.e., included in the labeling), whether or not the event is anticipated because of the pharmacologic properties of the study agent.

• **Serious Adverse Experience (SAE)**: [ICTDR Investigator Manual, 2003]

  Any adverse experience occurring at any dose that results in any of the following outcomes:
  a. **Death**
  b. **Life threatening** – defined as an experience that places the patient or subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred. (Note: this does not include a reaction that, had it occurred in a more severe form, might have caused death)
  c. Requires inpatient **hospitalization** or prolongation of existing hospitalization
  d. Results in a **congenital** anomaly or birth defect
  e. Results in a **persistent or significant disability** or incapacity
  f. **Important medical events** that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Following Scales were used for evaluation of Global Functioning, Disease Psychopathology, Disease Severity & Improvement, and Subjective Wellbeing:

**GAF (Global Assessment of Functioning) Scale** [In - DSM IV, Washington DC, American Psychiatric Association, 1994; Rush AJ et al, 2009; Sajotovic M and Ramirez LF, 2003] (Appendix - XI)

Rating of overall psychological, social and occupational functioning was done through GAF (Global Assessment of Functioning) Scale – a 100 point continuous scale divided in to 10 ranges (each range consisting of 10 points) of functioning.

**PANSS (Positive and Negative Syndrome Scale)** [Kay SR et al, 1987] (Appendix - IX)

The PANSS or the Positive and Negative Syndrome Scale is a medical scale used for measuring symptom severity of patients with schizophrenia. It was published in 1987 by Stanley Kay, Lewis Opler, and Abraham
Fiszbein. It is widely used in the study of antipsychotic therapy. The name refers to the two types of symptoms in schizophrenia, as defined by the American Psychiatric Association.

The PANSS was developed as a more rigorous and objective method for evaluating positive, negative and other symptom dimensions in schizophrenia. The PANSS assessment is derived from behavioral information collected from a number of sources including observations during the interview, a clinical interview, and reports by primary care or hospital staff or family members.

PANSS has total 30 item: 7 positive, 7 negative, and 16 general psychopathology symptom items. The Positive scale include 7 items: Delusions, Conceptual disorganization, Hallucinations, Hyperactivity, Grandiosity, Suspiciousness/persecution and Hostility. The Negative scale include 7 items: Blunted affect, Emotional withdrawal, Poor rapport, Passive/apathetic social withdrawal, Difficulty in abstract thinking, Lack of spontaneity and flow of conversation, Stereotyped thinking. The General Psychopathology scale include 16 items: Somatic concern, Anxiety, Guilt feelings, Tension, Mannerisms and posturing, Depression, Motor retardation, Uncooperativeness, Unusual thought content, Disorientation, Poor attention, Lack of judgment and insight, Disturbance of volition, Poor impulse control, Preoccupation, Active social avoidance.

PANSS is a 7 point severity scale. Each of the 30 items is accompanied by a specific definition as well as detailed anchoring criteria for all seven rating points. These seven points represent increasing levels of psychopathology, as follows: 1- absent, 2- minimal, 3- mild, 4- moderate, 5- moderately severe, 6- severe, 7- extreme.

Range of possible scores 30-210 (positive and negative symptom groups are often reported separately; both score 7-49).

Clinical Global Impression (CGI) Scale (Guy W, 1976) (Appendix - X)
The Illness (disease) severity status as defined in CGI-S (Clinical Global Impressions of Severity) Scale. The CGI scale refers to the global impression of the patient and requires clinical experience with the syndrome under assessment. The CGI improvement scale can be completed only following or during treatment. The concept of improvement refers to the clinical distance between the individual's current condition and that prior to the start of treatment. The scale has a single item measured on a 7 point scale from 1 (‘normal’, not ill) to 7 (extremely ill).

Subjective well-being (SW) 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 Subjective Well-being of the Patient under...
Antipsychotic Treatment was rated through a 20-item Subjective Well-Being Under Neuroleptic Treatment Scale, SWN-20 scale (also known as SWN-K scale)

The increasing interest in subjective well-being and quality of life of schizophrenic patients shows a conceptual shift in therapeutic outcome criteria. Symptom reduction alone was the most essential outcome parameter for a long time; with the development of atypical antipsychotics more ambitious success criteria, including the patients’ perspective, are considered now. While effects on (positive) psychopathology do not differ markedly between typical and atypical antipsychotics, the lack of motor symptoms, the improvement of negative, affective and cognitive symptoms, and particularly the better subjective well-being as well as quality of life are major advantages for the new antipsychotic drugs.

Quality of life assessment is a new methodological approach to differentiate therapeutic effects. A number of disease-specific or generic scales have been used to measure quality of life of schizophrenic patients under antipsychotic treatment. There is strong evidence by seven controlled and eight open trials that in comparison to typical antipsychotics, atypicals improve the quality of life significantly, and the difference is of major clinical relevance in many patients.

SWN-20 is an instrument to measure the subtle subjective changes, such as restrictions in emotionality, the clarity of thinking and spontaneity, that are often referred as 'pharmacogenic depression' or the 'neuroleptic induced deficit syndrome'. The original version of SWN contained 38 items, but was later revised to a shortened version of 20 items, and was able to differentiate between atypical antipsychotics. SWN scores appear to correlate with measure of objective psychopathology, quality of life and other self-ratings of mood. It is a self-report scale developed in order to assess the well-being of patients receiving antipsychotic medication independent of the improvement in their psychotic symptoms. This tool has demonstrated good practicability, reliability, validity and sensitivity.

SWN-20 is a disease-specific patient-rated scale to evaluate the subjective well-being under neuroleptic (antipsychotic) treatment, which has five subdomains (regarding mental or cognitive functioning, self-control, emotional regulation, self control, physical functioning and social integration). The scale has 5 subscales Emotional Regulation, Self Control, Mental Functioning, Social Integration and Physical Functioning. Each subscale subdomain) has 4 items consisting 2 positive and 2 negative items. It is a six point Likert scale. The total score ranges from 20-120, higher scores implying higher subjective well-being. There are 20 items (question/parameter) given to assess subjective well-being under the neuroleptic treatment given to the patient. Each of the 20 items are graded in to 6 response options such as Not at all or A little or Some-what or Noticeable or Much or Very Much - as applied to individual patient. The majority of patients are able to complete the SWN-20 (or SWN-K) in a reliable and consistent manner.

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Before undertaking the study, the scale was first translated in regional language, was retranslated back in English and also was prevalidated in schizophrenic patients and appropriate corrections were made.

Severity (intensity) of Certain Common and Expected Adverse Events such as Antipsychotic-induced Extrapyramidal side effects, Weight gain, Glucose and Lipid abnormalities was graded as follows:

The Antipsychotic-Induced Extrapyramidal Side Effects (such as salivation, slurring in speech, tremors, dystonia, dyskinesia, rigidity, akathisia) were rated through ESRS (Extrapyramidal Symptom Rating Scale) having individual symptom severity grading from 0 to 6 (absent to extremely severe) (Chouinard G, et al., 1980) (Appendix VIII)

**Weight gain or loss: (if increase/decrease from baseline value)** (DAIDS table for grading the severity of adult and pediatric adverse events, v1.0, 2004, clarification Aug 2009)

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to 10 %</td>
<td>&gt; 10 to 20 %</td>
<td>&gt; 20 %</td>
<td>---</td>
</tr>
</tbody>
</table>

**BMI (graded as per Asian Indian standards)** (Misra A et al 2009)

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 to 24.9 Kg/m²</td>
<td>≥ 25 to 37.4 Kg/m²</td>
<td>≥ 37.5 Kg/m²</td>
<td>---</td>
</tr>
</tbody>
</table>

**Fasting Blood Glucose and Lipid Changes** (if higher than baseline value): (DAIDS table for grading the severity of adult and pediatric adverse events, v1.0, 2004, clarification Aug 2009)

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>110 to 125 mg/dL</td>
<td>126 to 250 mg/dL</td>
<td>251 to 500 mg/dL</td>
<td>&gt; 500 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>200 to 239 mg/dL</td>
<td>&gt; 240 to 300 mg/dL</td>
<td>&gt; 300 mg/dL</td>
<td>NA</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>NA</td>
<td>&gt; 500 to 750 mg/dL</td>
<td>&gt; 751 to 1200 mg/dL</td>
<td>&gt; 1200 mg/dL</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>130 to 159 mg/dL</td>
<td>&gt; 160 to 190 mg/dL</td>
<td>&gt; 190</td>
<td>NA</td>
</tr>
</tbody>
</table>

*HDL cholesterol was not graded for severity. In case of Triglyceride > ULN lab value (165) to 500 was graded as mild (ULN= Upper limit of normal)

**Hypotension** (DAIDS table for grading the severity of adult and pediatric adverse events, v1.0, 2004, clarification Aug 2009)

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>Symptomatic, corrected with oral fluid replacement</td>
<td>Symptomatic, IV fluids indicated</td>
<td>Shock, requiring use of vasopressors or mechanical assistance to maintain blood pressure</td>
</tr>
</tbody>
</table>

**Hematology** (DAIDS table for grading the severity of adult and pediatric adverse events, v1.0, 2004, clarification Aug 2009)

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin reduction</td>
<td>10.0 – 10.9 g/dL</td>
<td>9.0 – 9.9 g/dL</td>
<td>7.0 – 8.9 g/dL</td>
</tr>
<tr>
<td>White Blood Cell count decrease</td>
<td>2,000 – 2,500/mm³</td>
<td>1,500 – 1,999 /mm³</td>
<td>1,000 – 1,499/mm³</td>
</tr>
<tr>
<td>Platelets count decrease</td>
<td>100,000 – 124,999/mm³</td>
<td>50,000 – 99,999/mm³</td>
<td>25,000 – 49,999/mm³</td>
</tr>
</tbody>
</table>
The Clinical AEs (including Extrapyramidal Side Effects) were rated as per 4-point severity (intensity) grading given below: (DMID interventional protocol template, v3.0, 28 May 2007)

**Mild (Grade 1)** - events require minimal or no treatment and do not interfere with the patient’s daily activities.

**Moderate (Grade 2)** - events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

**Severe (Grade 3)** - events interrupt a patient’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

**Life threatening (Grade 4)** - any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

### Causality Assessment:

The evaluation of the likelihood that a medicine is the causative agent of an observed adverse reaction.

Causal relationship with the investigational study treatment was assessed using the following WHO-UMC Causality categories (WHO-Uppsala Monitoring Centre, 2000).

<table>
<thead>
<tr>
<th>Causality term</th>
<th>Assessment criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Certain</strong></td>
<td>• Clinical event or laboratory test abnormality, with plausible time relationship to drug intake, which</td>
</tr>
<tr>
<td></td>
<td>• Cannot be explained by disease or other drugs</td>
</tr>
<tr>
<td></td>
<td>• Response to withdrawal (dechallenge) clinically plausible</td>
</tr>
<tr>
<td></td>
<td>• Event must be definitive pharmacologically or phenomenologically using suitable rechallenge procedure, if necessary</td>
</tr>
<tr>
<td><strong>Probable/Likely</strong></td>
<td>• Clinical event or laboratory test abnormality, with reasonable time sequence to drug intake, which</td>
</tr>
<tr>
<td></td>
<td>• Unlikely to be attributed to concurrent disease or other drugs</td>
</tr>
<tr>
<td></td>
<td>• Response to withdrawal (dechallenge) clinically reasonable</td>
</tr>
<tr>
<td></td>
<td>• Rechallenge information not necessary</td>
</tr>
<tr>
<td><strong>Possible</strong></td>
<td>• Clinical event or laboratory test abnormality, with reasonable time sequence to drug intake, which</td>
</tr>
<tr>
<td></td>
<td>• Could also be explained by concurrent disease or other drugs</td>
</tr>
<tr>
<td></td>
<td>• Information on drug withdrawal may be lacking or unclear</td>
</tr>
<tr>
<td><strong>Unlikely</strong></td>
<td>• Clinical event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable</td>
</tr>
<tr>
<td></td>
<td>• Disease or other drugs provide plausible explanations</td>
</tr>
<tr>
<td><strong>Conditional/ Unclassified</strong></td>
<td>• Clinical event or laboratory test abnormality about which</td>
</tr>
<tr>
<td></td>
<td>• More data for proper assessment needed, or</td>
</tr>
<tr>
<td></td>
<td>• Additional data is under examination</td>
</tr>
<tr>
<td><strong>Unassessable/ Unclassifiable</strong></td>
<td>• Report suggesting an adverse reaction which</td>
</tr>
<tr>
<td></td>
<td>• Cannot be judged because information is insufficient or contradictory</td>
</tr>
<tr>
<td></td>
<td>• Data cannot be supplemented or verified</td>
</tr>
</tbody>
</table>
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3.5. Study Flow Chart

<table>
<thead>
<tr>
<th>Visit</th>
<th>Week</th>
<th>Day</th>
<th>Purpose</th>
<th>Antipsychotic Medication</th>
<th>Concomitant Medication</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-0 to 2</td>
<td>-(0 to 14)</td>
<td>Screening*</td>
<td>Yes</td>
<td>Record</td>
<td>Diagnosis, Inclusion/Exclusion Criteria evaluation, Informed consent, Personal history &amp; Physical examination, Psychiatric evaluation, Lab tests &amp; Urine pregnancy test in women of child-bearing age</td>
</tr>
<tr>
<td>1</td>
<td>Week 2</td>
<td>1 +/-3 days*</td>
<td>Baseline*</td>
<td>Yes</td>
<td>Record</td>
<td>Enrolment based on clinical criteria, Verification of Inclusion/Exclusion criteria, weight, pulse and B P measurement, Psychiatric evaluation, Adverse events monitoring</td>
</tr>
<tr>
<td>2</td>
<td>Week 4</td>
<td>As per scheduled visit day +/-3 days*</td>
<td>Follow up</td>
<td>Yes</td>
<td>Record</td>
<td>Weight, Psychiatric evaluation, Adverse events monitoring</td>
</tr>
<tr>
<td>3</td>
<td>Week 8</td>
<td>&quot;</td>
<td>Follow up</td>
<td>Yes</td>
<td>Record</td>
<td>Weight, Psychiatric evaluation, Adverse events monitoring</td>
</tr>
<tr>
<td>4</td>
<td>Week 12</td>
<td>&quot;</td>
<td>Follow up</td>
<td>Yes</td>
<td>Record</td>
<td>Weight, pulse and B P measurement, Psychiatric evaluation, Adverse events monitoring, Lab tests &amp; Urine pregnancy test in women of child-bearing age</td>
</tr>
<tr>
<td>5</td>
<td>Week 16</td>
<td>&quot;</td>
<td>Follow up</td>
<td>Yes</td>
<td>Record</td>
<td>Weight, Psychiatric evaluation, Adverse events monitoring</td>
</tr>
<tr>
<td>6</td>
<td>Week 20</td>
<td>&quot;</td>
<td>Follow up</td>
<td>Yes</td>
<td>Record</td>
<td>Weight, Psychiatric evaluation, Adverse events monitoring</td>
</tr>
<tr>
<td>7</td>
<td>Week 24</td>
<td>&quot;</td>
<td>Follow up</td>
<td>Yes</td>
<td>Record</td>
<td>Weight, pulse and B P measurement, Psychiatric evaluation, Adverse events monitoring &amp; Urine pregnancy test in women of child-bearing age</td>
</tr>
<tr>
<td>8</td>
<td>Week 30</td>
<td>&quot;</td>
<td>Follow up</td>
<td>Yes</td>
<td>Record</td>
<td>Weight, Psychiatric evaluation, Adverse events monitoring</td>
</tr>
<tr>
<td>9</td>
<td>Week 36</td>
<td>&quot;</td>
<td>Follow up</td>
<td>Yes</td>
<td>Record</td>
<td>Weight, pulse and B P measurement, Psychiatric evaluation, Adverse events monitoring</td>
</tr>
<tr>
<td>10</td>
<td>Week 42</td>
<td>&quot;</td>
<td>Follow up</td>
<td>Yes</td>
<td>Record</td>
<td>Weight, Psychiatric evaluation, Adverse events monitoring, Lab tests &amp; Urine pregnancy test in women of child-bearing age</td>
</tr>
<tr>
<td>11</td>
<td>Week 48</td>
<td>&quot;</td>
<td>Follow up</td>
<td>Yes</td>
<td>Record</td>
<td>Weight, pulse and B P measurement, Psychiatric evaluation, Adverse events monitoring</td>
</tr>
</tbody>
</table>

- *Those patients who were already satisfactorily receiving risperidone or olanzapine or clozapine as monotherapy before screening and those patients diagnosed first time for schizophrenia who require antipsychotic and were prescribed risperidone or olanzapine or clozapine as monotherapy by psychiatrist were selected based on basic inclusion-exclusion criteria (including lab tests) of the study and were enrolled in the study on day 1 of the screening visit. For them it was the baseline visit (VI).
- # Working days
- *Investigations for metabolic effects (fasting- blood glucose & lipid profile) were recorded Urine Pregnancy Test in women of child bearing age done as a safety measure was documented. Any other abnormal findings for any other test if (as and when) directed by psychiatrist were documented.
Materials and Methods

Number of Visits: 11 Visits

Study Commencement
The study commenced at study centre after receiving following documents:
1. A written approval from the Institutional Ethics Committee of the hospital for final study protocol
2. Approval of Informed Consent Form & Patient Information Sheet in English and local Vernacular language by Institutional Ethics Committee
3. Baseline values for Laboratory Parameters obtained.

Study Duration:
Initiation At the time of enrollment of first patient at study.
Completion 48 weeks after enrollment of last patient at study
Depending upon the study selection criteria, the enrollment accomplished within six months from the commencement of the study.

3.6. Study End Points Evaluation:
Primary Outcome Measures:
1) The assessment of functioning and subjective wellbeing of patients receiving antipsychotic measured by GAF (Global Assessment of Functioning) Scale and SWN-20 (Subjective Well-being Under Neuroleptic Treatment – 20 items Scale)
2) The assessment of the tolerability (with focus on metabolic effects) of individual study antipsychotic by
   o Weight / Body mass index
   o Metabolic tests - fasting analytes for blood glucose and lipids
   o Extrapyramidal symptoms as measured by ESRS (Extrapyramidal Symptoms Rating Scale)
   o Treatment-emergent Adverse Events

Secondary Outcome Measures:
1) The assessment of the efficacy of study antipsychotic in improving psychopathology of schizophrenia at any time during the study as measured by (a) change in total PANSS (Positive and Negative Syndrome Scale) score from baseline, and (b) change in CGI-S (Clinical Global Impressions-Seventy) score from baseline The assessment of proportion of patients responding to study antipsychotic monotherapy at any time during study was done by reduction in total PANSS score from the baseline ≥ 20 % and change in score of CGI-I (Clinical Global Impressions-Improvement)
2) Time to all-cause medication discontinuation. The time until medication (treatment) discontinuation of study antipsychotics (risperidone or olanzapine or clozapine) in patients with schizophrenia for
any and specific cause. It was measured as the percentage of patients discontinuing study antipsychotics prior to 48 weeks for any and specific cause.

3.7. Investigations

Documentation of the investigations done as mentioned below during the observational phase was recorded in the Case Record Form (CRF).

- Fasting Blood Biochemistry Analytes
  - Blood glucose
  - Lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides,)
- Urine pregnancy test (in females of child-bearing age)
- Any other test(s), as and when directed and done by treating psychiatrist (and if abnormal were recorded in CRF)

In all the three therapeutic groups of patients, morning samples for the fasting blood biochemistry analytes i.e. fasting blood glucose and fasting lipid profile were collected by calling the outdoor patients with overnight fasting of 10 hours. These samples were analysed with fully automated, random access ‘BS-200 Chemistry Analyzer’

In the child-bearing age females, the urine pregnancy test as a safety measure was carried out by using ‘One-Step HCG Urine Pregnancy Test Device’ (manufactured by IND Diagnostic Inc, Canada) with HCG sensitivity of 20 micro-liter/mL and which gives end result within 5 minutes.

Additionally in clozapine group, periodical blood counts were done by using fully automated 3-part haematology analyzer ‘BC 3000 Plus’ and 12-lead ECG was done using single-channel ECG cardiograph machine (BPL Cardiart 108T) at screening and end-point visits.

3.8. Statistical Analysis of Data

This comprised all schizophrenic patients who were diagnosed (as per DSM IV criteria) and being treated by psychiatrists with atypical antipsychotics purely based on their clinical experience and judgment and fall in to three monotherapy antipsychotic treatment groups meeting defined inclusion-exclusion criteria (only for the purpose of qualifying for observational study), and who have had at least one administration of prescribed medication as well as at least one follow-up efficacy measurement/evaluation. The patients not completing the study (including dropouts during the treatment due to any reason or lost-to-follow up > 3 consecutive scheduled visits but had taken at least one dose of treatment medication and had one post-baseline evaluation (intent-to-treat set) were included for analysis. This consisted analytical sample of total 154 patients in these patients, last observation carried forward was used.
Materials and Methods

The visit 1 at the time of enrollment was considered as baseline visit. The end-of study scores were considered as the end-point scores. Data for GAF, ESRS, SWN-20, PANSS and CGI scores, and data for vital signs (e.g. pulse, B P), anthropometric data (e.g weight/B.M.I.) and adverse events were obtained at baseline and at scheduled time-points based on assessment schedule. Data of laboratory tests (fasting blood glucose and lipids) were obtained as per assessment schedule for the three antipsychotic medications receiving groups. For all these data, the following statistical analysis was performed.

The Shapiro-Wilk test, Histograms, Q-Q plots and Side-by-side Box plots were used to assess normality of the data of the three therapeutic groups. In descriptive statistics, quantitative variables were expressed as mean ± SD for each scheduled time-point and categorical data were expressed in terms of proportion of percentage (%). Since the smaller sample size in clozapine (n=5) group renders it to be sensitive in case of descriptive statistics, the use of inferential statistics while comparing it with risperidone (n=87) group and olanzapine (n=62) group was found appropriate.

In inferential statistics, considering the non-parametric data distribution, Kruskal-Wallis H Nonparametric ANOVA was performed for between-group comparison for the baseline and endpoint assessments. If 2-tailed p value was < 0.05, in case of baseline and endpoint between-group assessments, Mann Whitney U Test was further applied as post-hoc test. In case of within-group comparisons, Friedman’s Repeated Measure Nonparametric ANOVA was performed in case of biochemical laboratory parameters (fasting glucose, lipids) for the corresponding evaluation visits i.e. baseline, week 12 and endpoint, and in case of rest of the parameters for baseline, quarterly evaluation visits (week 12, week 24, week 36) and for endpoint was performed. In case of 2-tailed p value < 0.05, the post-hoc analysis (Wilcoxon Signed Rank Test) was further applied to assess within-group statistical difference. And in case of p value < 0.05 obtained in Wilcoxon Signed Rank Test in two (out of three) groups further to assess the between-group difference Mann Whitney U test was also done. For assessing time-to-discontinuation of treatment, Kaplan Meir Survival Curves were used. Clinically significant endpoint-weight gain (≥7%) was assessed in three therapeutic groups by applying Kruskal-Wallis H Nonparametric ANOVA and by plotting the graph for ≥7% weight gain in three therapeutic groups. Clinically significant biochemical abnormalities in three therapeutic groups (for scheduled time-points) were presented in terms of proportion of percentage (%). The analysis of number of patients clinically improved at endpoint (clinical response/improvement in case of reduction of ≥20% in Total-PANSS score from the baseline) after treatment were expressed as percentage N (%N). For assessing the correlation between quality of life (SWN-20) and its five subscales with PANSS and its three subscales and global functioning (GAF), the Spearman’s Rank Correlation Coefficient (rho) was applied. Drug-induced extrapyramidal side effects (EPS) assessed with ESRS score were interpreted clinically and...
categorized with respect to 3 grades of severity, and were presented in terms of proportion of percentage (%).

Adverse events were presented by frequency analysis with respect to incidence, severity as well as WHO causality grades. This was done in all the patients included in the observational study (n=168, safety set). All the statistical tests were interpreted at the 5% significance level and 2-tailed p-value < 0.05 were considered to be statistically significant.

3.9. Ethical Considerations

Patient Information and Consent

Informed written consent was obtained from each patient or his/her authorized legal representative in the form provided after providing detailed information about the proposed study. Those who refused to give written informed consent were not included in the study. The investigators gave each patient, full information about the nature, meaning and importance of the study and description of the procedures to be followed by the investigator in accordance with GCP guidelines. Patients were also told that they have the right to opt out of the study at any time without having to give reasons if they so wish and without prejudice to further treatment. The patient/guardian was given sufficient time to consider the implications of the study before deciding whether or not to participate in the study. The patient or his/her authorized legal representative and the clinical investigator signed the informed consent form. If the patient was unable to comprehend and understand the necessary information pertaining to his/her participation in the study, consent of legal guardian were obtained.

Confidentiality

The identity of patients and data generated in the study were handled in strict confidence. Data were made available only to team members involved in the study and to institutional ethics committee.

Ethics Committee

The study was carried out according to the protocol approved by the Institutional Ethics committee (IEC) of the hospital. The study was conducted in accordance with the “Declaration of Helsinki”, “ICH- Good Clinical Practice” guidelines, and Guidelines of ICMR.
3.10 Tests for Estimation of Biochemical Parameters

Blood Glucose Estimation
Principle of estimation: Enzymatic colorimetric method - Glucose Oxidase/Peroxidase (GOD/POD) method.
Analytical Instrument Used: A fully automated Clinical Chemistry Analyzer - BS-200 - of Agappe Diagnostics Ltd.

Blood Lipid Profile Estimation
For fasting lipid profile estimation, following tests were performed
1) Total Cholesterol, 2) LDL-C, 3) HDL-C, 4) VLDL: TG/5, 5) Triglycerides, 6) Total lipids

1) Total Cholesterol
Principle of Estimation: Direct Enzymatic colorimetric method
Analytical Instrument Used: A fully automated Clinical Chemistry Analyzer - BS-200 - of Agappe Diagnostics Ltd.

2) LDL (Low Density Lipoprotein) Cholesterol
Principle of Estimation: Direct Enzymatic colorimetric method
Analytical Instrument Used: A fully automated Clinical Chemistry Analyzer - BS-200 - of Agappe Diagnostics Ltd.

3) HDL (High Density Lipoprotein) Cholesterol
Principle of Estimation: Direct homogenous enzymatic colorimetric method
Analytical Instrument Used: A fully automated Clinical Chemistry Analyzer - BS-200 - of Agappe Diagnostics Ltd.

4) Triglycerides
Principle of Estimation: Direct Enzymatic colorimetric method
Analytical Instrument Used: A fully automated Clinical Chemistry Analyzer - BS-200 - of Agappe Diagnostics Ltd.

3.11. Tests for Other Parameters

Serum Prolactin
Method and Principle: Quantitative Determination of Prolactin (PRL) Hormone in Human Serum by a Microplate Chemiluminescence Immunoenzymometric Assay (CLIA) The analytical instrument used was a fully automated Clinical Chemistry Analyzer - BS-200 - of Agappe Diagnostics Ltd. As the transient rise in PRL can occur even with drugs that rarely give chronic elevations, PRL was measured in the morning after advising the patient to skip the morning dose of antipsychotic.

Urine Pregnancy Test
In the child-bearing age females, the urine pregnancy test as a safety measure was carried out by using ‘One-Step HCG Urine Pregnancy Test Device’ (manufactured by IND Diagnostic Inc., Canada). It is a rapid chromatographic immunoassay for the qualitative detection of human chorionic gonadotropin (hCG) in urine to aid in the early detection of pregnancy.
Sensitivity: The ‘One-Step hCG Urine Pregnancy Test Device’ (manufactured by IND Diagnostic Inc., Canada) has hCG sensitivity of 20 mIU/mL and which gives end result within 5 minutes.

Weight and Height Measurement

Weight measurement was done in kilogram (Kg) by using Analog Weighing Scale Machine. In the machine used, the markings on the dial are equally spaced between the numbers to indicate fractional amounts (smallest division or fraction measures up to ¼ i.e. 0.5 kg).

Standing height was measured with the help of height measurement scale in centimeters by measuring the maximum distance from the floor to the highest point on the head, when the subject is facing directly ahead. Footwear kept off, feet together, and arms by the sides. Heels, buttocks and upper back kept in contact with the wall when the measurement was made.

Blood Count

In clozapine therapeutic group, periodical blood counts (including Hb., RBC, Total WBC, Differential count) were performed as a safety measure.

The instrument used was fully automated 3-part Haematology Analyzer - ‘BC 3000 Plus’.

Electrocardiogram (ECG)

In clozapine therapeutic group, as a part of the screening and the end-point procedures, 12-lead ECG was done using single-channel electrocardiograph (ECG) machine (BPL Cardiart 108T).

Pulse and Blood Pressure (B.P.) Measurement

Radial Pulse and B.P. measurement was done per scheduled assessment visit (and as and when clinically needed). B.P. measurement was done with the help of Diamond branded Mercury B.P. instrument with accuracy of B.P. measurement up to smallest fraction of 2 mm of Hg. Participants were seated quietly for 5 minutes, with the arm supported at heart level.

In case of complaint/symptom requiring assessment for orthostatic (postural) hypotension. After 5 minutes of lying down, B.P. measurement first in supine position with the arm supported at the heart level, the B.P. cuff left in place; then allowing the patient to stand (with assistance if necessary with due safety care), and B.P. retaken within 3 minutes of quiet standing with the arm supported at the heart level and helping the patient to sit or lie down.