ABSTRACT: INTRODUCTION: Schizophrenia is a chronic debilitating disease with significant morbidity and mortality that often requires either typical or atypical antipsychotic pharmacotherapy. Atypical antipsychotic drugs are preferred over typical because of lower risk of extra pyramidal side effects (EPS). As there is paucity of data in Indian population, the present study was taken up. OBJECTIVE: To evaluate the efficacy of haloperidol (Typical) and olanzepine (Atypical) antipsychotic drugs in schizophrenic patients. METHODS: It was a comparative study conducted on 60 patients of Schizophrenia for one year at Department of Psychiatry, Victoria Hospital, Bangalore. The study subjects were randomly assigned into 2 groups of 30 patients each, where group 1 were treated with atypical antipsychotic drug olanzapine and group 2 with typical antipsychotic drug Haloperidol and both groups received the treatment for one year. Efficacy was measured using Positive and negative syndrome scale (PANSS), Clinical Global Impression – Severity of illness (CGI-S), Clinical Global Impression – Improvement (CGI-I) scales. RESULTS: Both typical and atypical antipsychotics were associated with comparable baseline to endpoint reduction in symptom severity. However atypical antipsychotic drug olanzapine treated subjects had significantly greater decrease in symptom severity as measured by PANSS negative score and total score, CGI-S scale and CGI-I scale. KEYWORDS: Efficacy, Olanzapine, Haloperidol, Schizophrenia, Treatment.

INTRODUCTION: Schizophrenia is a severe mental disorder characterized by delusions, hallucinations, incoherence and physical agitation.1 Schizophrenia affects 1% of the population and ranks among the top 10 causes of disability worldwide; in India prevalence is 2.3/1000 population and thus it imposes a heavy burden on the patient, their family and society.2 It is a heterogeneous psychiatric disorder in which multiple neurotransmitter system has been implicated; increased and decreased dopamine transmission in the sub cortical mesolimbic and mesocortical system is closely linked to the positive and negative symptoms of schizophrenia, respectively. Serotonin, acetylcholine and glutamate are other neurotransmitter implicated in its pathogenesis. The core features of Schizophrenia include positive, negative, cognitive and affective symptoms. Positive symptoms include delusions, hallucinations, grossly disorganised thought, and agitation. Negative symptoms include alogia, flattened affect, anhedonia and avolition. While positive symptoms are most amenable to the treatment there is no effective treatment available for negative and cognitive symptoms.2 Disease course is variable and mostly chronic, characterized by ongoing functional impairment and the frequent recurrence of acute psychotic symptoms. Thus, the general goals of the treatment are to quickly reduce symptoms severity, improve patient functioning, prevent recurrences of the symptomatic episodes and associated deterioration of the functioning.3
It is a chronic debilitating disease with significant morbidity & mortality that often requires antipsychotic pharmacotherapy for life. The treatment of schizophrenia remains an enormous challenge. Typical antipsychotic medications like haloperidol, chlorpromazine and trifluperazine are shown to suppress the acute psychotic symptoms of schizophrenia and prevent their recurrence. However, many patients with chronic disorders were found to be unresponsive to these antipsychotic drugs, and it was generally believed that, despite the ability of these drugs to suppress acute psychotic symptoms and prevent relapse, they did not positively change the long-term course of the disorder or subsequently improve outcome.

Introduction of atypical antipsychotics like risperidone, olanzapine and clozapine have been heralded as a therapeutic advance in its management, accounting for over 2/3rd of all antipsychotic drug prescription. Atypical antipsychotics affect a broader range of Schizophrenic psychopathology and are generally better tolerated than conventional antipsychotics.4,5

Studies comparing typical and atypical antipsychotic drug showed equal efficacy or, at most modest therapeutic superiority for the atypical drug in positive, negative, cognitive and mood symptoms, have lower risk of extra pyramidal adverse effects, which improves patient compliance. But it needs to be balanced against the problems of weight gain, dyslipidemia and hyperglycaemia which constitute part of metabolic syndrome.5,6

As there is paucity of data in Indian population the present study has been taken up to evaluate the efficacy, tolerability and treatment adherence of commonly prescribed typical and atypical antipsychotics in schizophrenic patients in a tertiary care hospital.

METHODOLOGY:

SOURCE OF DATA: Outpatients and inpatients in the department of psychiatry, Victoria hospital, Bangalore.

METHODS OF COLLECTION OF DATA:

Study Design: Prospective observational study.
Study Period: Jan 2010- June 2011.
Sample Design: Purposive sampling
Sample Size: 60 patients with schizophrenia.

- After obtaining approval and clearance from the institution ethical committee, patients were included for the study.
- The study subjects fulfilling the inclusion/exclusion criteria were randomly assigned into 2 groups of 30 patients in each group.
- Group 1: Patients treated with olanzapine (oral dose 2.5 mg to 20 mg).
- Group 2: patient treated with haloperidol (oral doses 1 mg to 10 mg).

Inclusion Criteria:

- Patients of either sex aged between 18-65years suffering from schizophrenia.
- Patients who fulfilled the criteria of ICD-10 (International Classification of Disease-10, WHO1992).
- Patients in the respective groups who were on treatment with that particular drug for a minimum duration of 3months.
- Patients who gave Written informed consent.
Exclusion Criteria: Patients who received more than one antipsychotic medication and who had received them in the past one year:
   - Patient with major psychiatric illness.
   - Patients with co-morbid medical conditions like Diabetes mellitus, Dyslipidemia, Coronary heart disease, Hypertension, Parkinson disease.
   - Patient with concomitant physical illness.
   - Presence of alcohol and substance abuse/dependence, epilepsy, mental retardation, mental disorders other than schizophrenia.
   - Patient suffering from any major endocrine disorders.
   - Pregnant and lactating women.
   - Non-compliant patients who were unable to give consent for the study.

Study Procedure: Inpatients as well as outpatients at the department of psychiatry diagnosed to be suffering from schizophrenia using ICD-10 criteria and fulfilling the inclusion/ exclusion criteria were taken into the study after obtaining written informed consent.

Efficacy was assessed by:
   - Positive and negative syndrome scale (PANSS) (Annexure-1).
   - Clinical global impression- severity of illness (CGI-S) (Annexure-2).
   - Clinical global impression- global improvement (CGI-I) (Annexure-3).

The detailed schedule of patient visit is as follows:
Visit 1/ day1/ initial or baseline assessment:
   - Details of patient’s demographic characteristic, medical history, concomitant medication, pill count and detailed physical/psychiatric evaluation were recorded.
   - Blood samples for relevant baseline laboratory investigations were collected.
   - Patients were issued medication once every month and instructed for regular follow up thereafter.
   - Patients were clinically assessed once in 3 months and relevant laboratory.

Visit 2/ 3rd month:
   - Medication compliance, pill count, any intercurrent illness or change in concomitant medications were recorded.
   - All observed or spontaneously volunteered adverse events were recorded.
   - A thorough physical/ psychiatric evaluation was carried out and recorded.

Visit 3/ 6th month:
   - Medication compliance, pill count, any intercurrent illness or change in concomitant medication were recorded.
   - All observed or spontaneously volunteered adverse events were recorded.
   - A thorough physical/ psychiatric evaluation was carried out and recorded.
   - Blood samples for relevant laboratory investigations were collected.
Visit 4/ 9th month:
- Medication compliance, pill count, any intercurrent illness or change in concomitant medications were recorded.
- All observed or spontaneously volunteered adverse events were recorded.
- A thorough physical/ psychiatric evaluation was carried out and recorded.

Visit 5/ 1 year:
- Medication compliance, pill count, any intercurrent illness or change in concomitant medications were recorded.
- All observed or spontaneously volunteered adverse events were recorded.
- A thorough clinical/ psychiatric examination was repeated.
- Blood samples for relevant laboratory investigations were collected.

STATISTICAL METHODS: Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made,

ASSUMPTIONS:
1. Dependent variables should be normally distributed.
2. Samples drawn from the population should be random, and Cases of the samples should be independent.

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Post-hoc Tukey test and Bonferroni correction test has been performed.

SIGNIFICANT FIGURES:
+ Suggestive significance (P value: 0.05<P<0.10).
* Moderately significant (P value: 0.01<P ≤ 0.05).
** Strongly significant (P value: P≤0.01).

RESULTS:

<table>
<thead>
<tr>
<th>Psychiatric evaluation</th>
<th>Group I (olanzapine)</th>
<th>Group II (haloperidol)</th>
<th>P value</th>
<th>Group wise Comparison I-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 1</td>
<td>31.80±6.58</td>
<td>33.73±5.33</td>
<td>0.063+</td>
<td>0.423</td>
</tr>
<tr>
<td>Visit 2</td>
<td>27.87±5.94</td>
<td>27.70±5.33</td>
<td>0.360</td>
<td>0.992</td>
</tr>
<tr>
<td>Visit 3</td>
<td>24.00±5.35</td>
<td>22.13±4.37</td>
<td>0.259</td>
<td>0.292</td>
</tr>
<tr>
<td>Visit 4</td>
<td>21.60±5.13</td>
<td>17.80±4.01</td>
<td>0.007**</td>
<td>0.005**</td>
</tr>
<tr>
<td>Visit 5</td>
<td>19.53±5.04</td>
<td>13.73±3.83</td>
<td>&lt;0.001**</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>
Table 1: Psychiatric evaluation of study subjects by positive & negative symptom score

Table 1 summarizes changes in the positive & negative symptom score among the study subjects.

POSITIVE SCORE:
Group I, II: There is reduction in mean positive score at every visit compared to baseline scores. But there is significant difference in the mean positive score of visit 5 (at the end of one year) compared to baseline (p <0.001**). There was statistically significant reduction in positive score among two groups.

NEGATIVE SCORE:
Group I, II: There is reduction in mean negative score at every visit compared to baseline scores. But there is significant difference in the mean negative score of visit 5 compared to baseline (p <0.001**). There was statistically significant reduction in negative score among two groups.

GENERAL SCORE:
Group I, II: There is reduction in mean general score at every visit compared to baseline scores. But there is significant difference in the mean general score of visit 5 compared to baseline (p <0.001**). There was statistically significant reduction in general score among both groups. Group I showed strongly significant reduction in general score with p <0.001** in comparison to group II.

TOTAL SCORE:
Group I, II: There is reduction in mean total score at every visit compared to baseline scores. But there is significant difference in the mean total score of visit 5 compared to baseline (p <0.001**). Both the groups showed statistically significantly reduction in the positive score but atypical
antipsychotics particularly olanzapine showed significantly greater reduction in negative, general and total score with p <0.001**.

Fig. 1: Shows psychiatric evaluation of study subjects by positive symptom score

Fig. 2: Shows psychiatric evaluation of study subjects by negative symptom score

Fig. 3: Shows psychiatric evaluation of study subjects by total score
Psychiatric evaluation Group I (olanzapine) Group II (haloperidol) P value Group wise comparison I-II
CGI-S
Visit 1 2.90±0.31 2.90±0.31 0.002** 1.000
Visit 2 2.53±0.51 2.27±0.45 0.014* 0.067+
Visit 3 2.30±0.47 1.87±0.51 0.001** <0.001**
Visit 4 1.97±0.18 1.40±0.49 <0.001** <0.001**
Visit 5 1.70±0.47 1.20±0.41 <0.001** <0.001**
CGI-I
Visit 1 2.00 2.00±0.00 0.372 1.000
Visit 2 2.00 1.93±0.25 0.551 0.519
Visit 3 1.90±0.31 1.63±0.49 0.031* 0.030*
Visit 4 1.30±0.47 1.13±0.35 0.278 0.285
Visit 5 1.00 1.00±0.00 0.132 1.000

Table 2: Psychiatric evaluation of study subjects by Clinical global impression scale

**CGI-S**: (Clinical Global Impression – Severity scale).

**Group I, II**: There is reduction in mean CGI-S score at every visit compared to baseline scores. But there is significant difference in the mean CGI-S score of visit 5 (at the end of one year) compared to baseline (p <0.001**). There was statistically significant reduction CGI-S in score among the both groups.

**CGI-I**: (Clinical Global Impression – Improvement scale)

**Group I, II**: There was mean reduction in CGI-I score at every visit compared to baseline scores. But the reduction in CGI-I score was not statistically significant in the both groups.

![Fig. 4: Shows psychiatric evaluation of study subjects by clinical global impression improvement scale](image-url)
DISCUSSION: The present observational comparative study on efficacy of commonly prescribed typical and atypical antipsychotic drugs in schizophrenia was conducted in Department of Psychiatry, Victoria hospital over a period of 1 year 6 months.

The present study included a total of 60 patients. Out of 60 patients, at follow up there were 3 drop outs in haloperidol group. These patients were excluded from the analysis and 3 new patients were included and the study was completed. Among 3 drop outs, 2 were non-compliant with the treatment due to extra pyramidal symptoms in visit 1 and 1 patient did not report for visit 2 follow up, it was not possible to ascertain the reason for the drop out.

The Positive and Negative Syndrome Scale (PANSS) is a scale used for measuring symptom severity of patients with schizophrenia. The PANSS is based on findings that schizophrenia comprises at least two distinct syndromes. The positive syndrome consists of productive symptoms, while the negative syndrome consists of deficit features. This distinction is useful when developing treatment plans because treatment can be focused on the type of symptoms the patient is experiencing. It is also useful when studying the effects of medication because it allows determining which type of symptoms is being affected. PANSS composes of 3 components: Positive (P), Negative (N) and cognitive or General Psychopathology (G). Positive syndrome is composed of symptoms such as delusions, hallucinations and disorganized thinking. Negative syndrome is characterized by deficits in cognitive, affective, and social functions, including blunting of affect and passive withdrawal. General Psychopathology is composed of many deficits in cognition such as disorientation, poor attention, lack of insight and active social avoidance.

Positive symptoms of schizophrenia are due to dopaminergic D2 over activity in meso-limbic region. In the present study there was mean decrease in positive symptom score from baseline to end of the study and there was statistically significant reduction in positive score among both groups.

Negative symptoms are due to dopaminergic D2 over activity in mesocortical region, over activity of D4 dopamine receptor, abnormal frontal lobe circuit and abnormal serotonin transporter gene. Negative symptoms impose great suffering on patients by impeding their rehabilitation and psychological functioning. Conventional D2 blocking agents lack therapeutic efficacy for negative symptoms and thus may explain their limitation in mediating the chronic course of schizophrenia.
Atypical antipsychotic are more effective in reducing negative symptoms compared to typical antipsychotic drugs because of their selective D2 blocking action in mesolimbic and mesocortical dopaminergic pathway. Other possible mechanisms are potent D4 antagonist activity—higher affinity for dopamine D4 receptor than D2 receptor, low affinity/fast dissociation at D2 receptor; this rapid dissociation allows it to be more responsive to endogenous dopamine, thereby permitting antipsychotic action and also potent 5HT2 receptor antagonist—higher affinity for 5HT2 receptor than D2 receptor. In our study there was reduction in negative score among both groups. Olanzapine showed statistically significant reduction in negative symptom score compared to haloperidol group. In our study there was statistically significant reduction in general score among both groups. Olanzapine group showed statistically significant reduction in general score in comparison to haloperidol.

There was statistically significant reduction in total score among both groups. Olanzapine group showed greater reduction in total score in comparison to haloperidol.

Psychiatric evaluation of study subjects by Clinical global impression scale. The Clinical Global Impression rating scales are commonly used measures of symptom severity, treatment response and the efficacy of treatment. The Clinical Global Impression—Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient’s illness at the time of assessment. The Clinical Global Impression—Improvement scale (CGI-I) is a 7 point scale, is used to assess how much the patient’s illness has improved or worsened relative to a baseline state at the beginning of the intervention. In our study there was statistically significant reduction in CGI-S score in both groups with no inter group variation.

In terms of efficacy, atypical antipsychotic drugs are more efficacious in ameliorating symptoms in Schizophrenia patients than typical antipsychotic drugs. Both groups showed statistically significantly reduction in the positive score and CGI-S score but atypical antipsychotics olanzapine showed significantly greater reduction in negative, general and total score with p < 0.001. But the reduction in CGI-I score was not statistically significant in both groups.

There are some limitations of the study as in this study we have not taken an account of age, gender distribution and socioeconomic status of patients, which may influence the treatment outcome. Also number of patients in each group is less which necessitates more extensive study taking large number of patients.

ACKNOWLEDGMENTS: We are thankful to Dr. C.R. Jayanthi (professor and head, department of pharmacology, BMCRI), Dr. H. Chandrashekar (professor and head, department of psychiatry, Victoria hospital, Bangalore) for their kind support thought the study. We are also thankful to Dr. Rekha, Dr manjula, for their continuous cooperation during present study.

ANNEXURE 1: POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) RATING CRITERIA.

General rating instructions: Data gathered from this assessment procedure are applied to the PANSS ratings. 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= moderate severe, 6= severe, 7= extreme.
### PANSS RATING FORM:

<table>
<thead>
<tr>
<th>Positive scale</th>
<th>Absent</th>
<th>Minimal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Moderate severe</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1 Delusions</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>P2 Conceptual disorganization</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>P3 Hallucinatory behaviour</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>P4 Excitement</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>P5 Grandiosity</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>P6 Suspiciousness / persecution</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>P7 Hostility</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

**P= Positive**

<table>
<thead>
<tr>
<th>Negative scale</th>
<th>Absent</th>
<th>Minimal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Moderate severe</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 Blunted affect</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>N2 Emotional withdrawal</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>N3 Poor rapport</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>N4 Passive/apathetic social withdrawal</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>N5 Difficulty in abstract thinking</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>N6 Lack of spontaneity &amp; flow of conversation</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>N7 Stereotyped thinking</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

**N= Negative**

<table>
<thead>
<tr>
<th>General scale</th>
<th>Absent</th>
<th>Minimal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Moderate severe</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 Somatic concern</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>G2 Anxiety</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>G3 Guilt feelings</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>G4 Tension</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>G5 Mannerisms &amp; posturing</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>G6 Depression</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>G7 Motor retardation</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>G8 Uncooperativeness</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>G9 Unusual thought content</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
ANNEXURE 2: CLINICAL GLOBAL IMPRESSION- SEVERITY OF ILLNESS SCALES (CGI-S):

| 1 | Normal, not at all ill |
| 2 | Borderline, mentally ill |
| 3 | Mildly ill |
| 4 | Moderately ill |
| 5 | Markedly ill |
| 6 | Severely ill |
| 7 | Among the most extremely ill patients. |

ANNEXURE 3: CLINICAL GLOBAL IMPRESSION – IMPROVEMENT SCALE (CGI-I):

| 1 | Very much improved |
| 2 | Much improved |
| 3 | Minimally improved |
| 4 | No change |
| 5 | Minimally worse |
| 6 | Much worse |
| 7 | Very much worse |

REFERENCES:


AUTHORS:
1. Lavanya N.
2. Naveen Kumar M.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pharmacology, Sree Narayana Institute of Medical Science, Chalakka, Ernakulam, Kerala.
2. Assistant Professor, Department of Pharmacology, Sree Narayana Institute of Medical Science, Chalakka, Ernakulam, Kerala.

FINANCIAL OR OTHER COMPETING INTERESTS: None

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Lavanya N,
Assistant Professor,
Department of Pharmacology,
Sree Narayana Institute of Medical Science,
Chalakka, Ernakulam-683594, Kerala.
E-mail: dr.lavanya.n@gmail.com

Date of Submission: 27/01/2015.
Date of Peer Review: 28/01/2015.
Date of Acceptance: 10/02/2015.
Date of Publishing: 17/02/2015.