Treatment Persistence Associated with Typical versus Atypical Antipsychotics among Out-patients with Schizophrenia

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Author’s contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

ABSTRACT

Aim: The chronic nature of schizophrenia usually demands uninterrupted treatment in order to maintain optimal clinical and functional outcomes. It has been speculated that patients receiving atypical antipsychotics may persist longer in treatment than those receiving typical antipsychotics because of the lower risk of inducing extra-pyramidal symptoms. This study aimed to compare treatment persistence among patients with schizophrenia receiving atypical versus typical antipsychotics after discharge from a psychiatric hospital in Lagos, south-west Nigeria.

Study Design and Methodology: A retrospective cohort study design. Clinical records of 162 patients with schizophrenia admitted to a public psychiatric hospital were extracted to determine their persistence with treatment over a period of one year after their discharge to out-patient clinic. Treatment persistence (time to all cause treatment discontinuation) was determined using the Kaplan-Meier Survival analyses. The log rank test compared persistence in treatment between patients receiving atypical versus typical antipsychotic medications.

Results: Only 27.1% persisted in treatment for six months, while 19.1% persisted for one year. The mean time to all cause treatment discontinuation was 17.3 (±1.5) weeks (95% C.I= 14.4-20.3).
The mean duration of treatment persistence for patients receiving typical antipsychotics was 16.7 (±2.7) weeks (95% C.I= 11.5-22.0), and 17.7 (±1.8) weeks (95% C.I= 14.2-21.2) for patients receiving atypical antipsychotics. There was no significant difference in treatment persistence between the two groups (p=0.762).

**Conclusion:** There is a poor rate of persistence in treatment among patients with schizophrenia, regardless of the class of antipsychotics received. Considering the negative consequences of non-persistence in treatment including increased risk of relapse, re-hospitalisation and suicide, there is a dire need for interventions to facilitate treatment persistence in schizophrenia.

*Keywords: Treatment persistence; medication adherence; compliance; antipsychotics; time to all-cause medication discontinuation, schizophrenia.*

**1. INTRODUCTION**

Schizophrenia is a severe disabling psychiatric disorder characterised by significant impairment in perception, affect, thought and cognition. About 1 in 100 persons suffer from schizophrenia globally [1]. Due to the chronic nature of schizophrenia, affected individuals are required to persist in treatment in order to ensure optimal symptom control, maintain remission and facilitate favourable long-term clinical outcomes [2].

Antipsychotics are the mainstay in the pharmacological management of schizophrenia, and are commonly categorised into two classes. First-generation antipsychotics also known as ‘typical antipsychotics’ emerged in the 1950s while second-generation anti-psychotics also known as ‘atypical antipsychotics’ were developed in the 1980s. Both typical and atypical anti-psychotics have been shown to be effective in ameliorating the positive and negative symptoms of psychosis, functioning and quality of life among patients suffering from schizophrenia [3-5]. Conversely, interruption in antipsychotic therapy has been associated with poor treatment outcomes including increased risk of relapse, re-hospitalisation, inappropriate use of emergency services, suicide and mortality [2,6-10].

The personal and socio-economic burdens of non-persistence in treatment are staggering, contributing significantly to the several billions of dollars of liability attributed to schizophrenia annually [11]. In spite of the grave consequences of non-compliance with treatment, studies have shown poor rates of treatment adherence or persistence among patients with schizophrenia in the long-term. Globally, the majority of available data indicate that less than half of patients with schizophrenia persist with treatment after one year of commencement of anti-psychotic medications [12-17].

The major comparative benefit of atypical antipsychotics over typical antipsychotics is the lesser likelihood of incidences of extra-pyrdidyal side effects and tardive dyskinesia associated with its usage [3-4]. Consequently, it was anticipated that this favourable side effect profile of second generation anti-psychotics would translate to better treatment adherence or persistence in comparison to first generation antipsychotics [7,18].

However previous studies have reported divergent findings regarding the association between class of antipsychotics and persistence in treatment. While several authors reported that patients receiving atypical antipsychotics are more likely to persist in treatment than patients receiving typical antipsychotic medications [19-21], other authors found no association between treatment persistence and antipsychotics [22-28].

A handful of studies have demonstrated high rates of default from treatment or non-adherence with treatment among patients with chronic psychiatric disorders in sub-Saharan Africa [30-33]. However, there is scarcity of local research focusing on persistence in treatment among patients with schizophrenia, or the relationship between class of antipsychotic medication and treatment persistence [34]. A recent retrospective study conducted in a University teaching hospital in south-west Nigeria found that only 24% of patients with schizophrenia persisted in treatment for one year [34]. There was no association between class of antipsychotic and treatment persistence [34]. Further research in multiple settings are required to substantiate the extent and determinants of treatment persistence among patients with schizophrenia in Nigeria, thereby informing appropriate interventions targeted at optimising persistence in treatment. The current study aimed to compare persistence in treatment between patients with schizophrenia receiving typical antipsychotics and those
receiving atypical antipsychotics after discharge from in-patient care to out-patient clinic in a Nigerian psychiatric hospital.

2. METHODOLOGY

The study was a retrospective cohort study conducted at the largest psychiatric service in Nigeria, Federal Neuro-Psychiatric Hospital Yaba Lagos, south-West Nigeria. Lagos is the largest metropolis in Africa with a population of about 15 million. The hospital has an in-patient facility with 500 beds and out-patient clinics attended by more than a thousand patients weekly.

The study population consist of patients with schizophrenia hospitalised over a six-month period between January and June 2012 and subsequently discharged to attend follow-up appointment at the out-patient clinic. As part of a larger study of clinical outcomes in patients with schizophrenia, the medical records were reviewed between October and December 2013 to track persistence in treatment over a period of one year after discharge from in-patient care to out-patient clinic. Inclusion criteria for recruitment into the sample included case-notes with documented diagnoses of schizophrenia by consultant psychiatrists according to the ICD-10 diagnostic criteria [35]. Patients less than 18 years and greater than 65 years were excluded from the sample.

Data extracted for each patient included age, gender, marital status, employment status, educational level, clinical diagnosis, number of episodes of illness, number of psychiatric hospitalisations, prescribed anti-psychotic medications (class e.g. typical or atypical, route of administration and dosage), and attendance of out-patient clinic appointment/prescription refill over a period of one year after discharge from the hospital (treatment persistence).

In consistence with previous research, treatment persistence was defined as the time to all-cause treatment discontinuation and calculated as the total number of consecutive weeks from the date of hospital discharge to the onset of the first treatment gap of > 14 consecutive days [14,19]. Treatment gap commenced from the date of the missed clinic appointment/prescription refill. Evidence has shown that medical records of clinic attendance/prescription refill highly correlate with pharmacy refill and these indices are valid indirect measures of treatment adherence [14,24,36].

At the study location, the standard protocol ensures that patients with schizophrenia receive take-home prescriptions for anti-psychotic medications, which are collected from the hospital pharmacy before discharge. The quantities of drugs prescribed are sufficient until the date of the scheduled follow-up appointment at the out-patient clinic. At each follow-up visit, prescriptions are refilled after consultation and documented in the clinical records. The oral typical antipsychotics available in the hospital are chlorpromazine, trifluperazine and haloperidol, while the atypical antipsychotics are olanzapine risperidone and clozapine. Institutional approval was obtained from the Research and Ethical Committee.

2.1 Statistical Analysis

Data was analysed with IBM- SPSS (version 20). Basic demographic and clinical data were subjected to appropriate descriptive analysis including frequencies, mean and standard deviation. The major outcome of interest was persistence in treatment which was determined using the Kaplan-Meier Survival analyses. Participants who had not dropped out of treatment before the end of the one year period of review were right censored. The log-rank test was used to compare treatment persistence between patients receiving typical versus atypical antipsychotics.

3. RESULTS

A total of 162 patients with schizophrenia discharged from the hospital to follow-up care in out-patient clinic constituted the sample. They consisted of 65 (40.1%) males and 97 (59.1%) females with a mean age of 38.7 (±11.4) years (Table 1). More than two-thirds (68.5%) were single, while 31.5% were married. The majority (63.4%) were unemployed, though 38.0% and 46.7% of the participants attained secondary and tertiary levels of education respectively.

About a third (33.1%) of the patients were undergoing treatment for the first episode of schizophrenia, while 26.1%, 19.1%, 7.0%, and 14.7% were being managed for the second, third, fourth, and fifth or more episodes respectively (Table 1). The mean number of episodes of schizophrenia was 2.5(±1.6). Nearly a fifth of the participants (18.5%) had only been hospitalised once on account of schizophrenia, 40.7% had been hospitalised twice, 21.6% had undergone three hospital admissions while the others (19.2%) had been hospitalised on four or more
occasions. Typical oral antipsychotics were prescribed for 61 (37.7%) of the patients, while 101 (62.3%) received atypical oral antipsychotics prescriptions.

By the end of the first month after discharge from the hospital, only 50% of patients with schizophrenia persisted in treatment based on the earlier defined criteria. Thereafter, persistence in treatment declined gradually to 45% at the end of the third month, and 27.1% by the 6th month. Only a fifth (19.1%) had not defaulted from treatment one year after discharge from the hospital.

The mean duration of treatment persistence among the patients with schizophrenia, as measured by mean time to all cause treatment discontinuation using the Kaplan-Meier survival analysis (Fig. 1) was 17.3 (±1.5) weeks (95% C.I= 14.4-20.3). The mean duration of treatment persistence for patients receiving typical antipsychotics was 16.7 (±2.7) weeks (95% C.I= 11.5-22.0), and 17.7 (±1.8) weeks (95% C.I= 14.2-21.2) for patients receiving atypical antipsychotics. A comparison of the survival times between patients receiving typical versus atypical antipsychotics using the log-rank (Mantel-cox) test revealed no statistically significant difference in treatment persistence (chi-square=0.092, p=0.762) between the two groups.

### Table 1. Socio-demographic and clinical characteristics of the patients in the sample N= 162

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>65</td>
<td>(40.1)</td>
</tr>
<tr>
<td>Female</td>
<td>97</td>
<td>(59.9)</td>
</tr>
<tr>
<td>Marital status</td>
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<tr>
<td>Married</td>
<td>51</td>
<td>(31.5)</td>
</tr>
<tr>
<td>Single</td>
<td>111</td>
<td>(68.5)</td>
</tr>
<tr>
<td>Employment status</td>
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<td></td>
</tr>
<tr>
<td>Employed</td>
<td>59</td>
<td>(36.6)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>102</td>
<td>(63.4)</td>
</tr>
<tr>
<td>Level of education</td>
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<td></td>
</tr>
<tr>
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<td>5</td>
<td>(3.3 )</td>
</tr>
<tr>
<td>Primary</td>
<td>18</td>
<td>(12.0)</td>
</tr>
<tr>
<td>Secondary</td>
<td>57</td>
<td>(38.0)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>70</td>
<td>(46.7)</td>
</tr>
<tr>
<td>Number of episodes</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>52</td>
<td>(33.1)</td>
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<tr>
<td>2</td>
<td>41</td>
<td>(26.1)</td>
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<td>≥5</td>
<td>23</td>
<td>(14.7)</td>
</tr>
<tr>
<td>Number of admissions</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>(18.5)</td>
</tr>
<tr>
<td>2</td>
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<td>(21.6)</td>
</tr>
<tr>
<td>≥4</td>
<td>27</td>
<td>(19.2)</td>
</tr>
</tbody>
</table>

### Survival Functions

![Fig. 1. Kaplan-Meier survival analysis curve comparing treatment persistence between patients using typical versus atypical antipsychotic medication](image)
4. DISCUSSION

This study compared persistence in treatment between patients with schizophrenia receiving typical antipsychotics and those receiving atypical antipsychotics, after discharge from a psychiatric hospital in Lagos, south-west Nigeria. There is currently scarcity of data on this subject in Nigeria and Africa. The predominance of unemployment and single marital status among the patients is consistent with previous findings globally and reflect the decline in occupational and social functioning associated with schizophrenia [1].

In the current study, less than a fifth of the patients persisted in treatment for one year after discharge from the hospital, while 27% and 45% were persistent until the 6th and 3rd month post-hospitalisation respectively. These results converge with recent findings among patients with first episode schizophrenia in Ibadan, south-west Nigeria where 32% persisted in treatment for six months while 24% persisted in treatment for one year [34]. Similarly, in Northern Nigeria, only 50.6% of patients attending a psychiatric hospital were adherent with follow-up appointments three months after discharge [31].

The global literature has also demonstrated low rates of persistence in treatment among patients with schizophrenia. In a study conducted in the U.S.A, nearly half of patients on atypical antipsychotics had discontinued treatment within two weeks of discharge from the hospital, and only 1% persisted in treatment after two years [11]. Another U.S study showed that only a third of patients with schizophrenia discharged from a public hospital persisted in follow-up until the third appointment [12]. More recently, Ascher-Svanum et al. [14] reported that only 53% of a sample of patients with schizophrenia in the United States of America persisted in treatment until the end of the first year. In Asia, 34% of patients receiving typical antipsychotics discontinued their medications within one month, in comparison to 26% of patients receiving atypical antipsychotics [15]. Only 17% of patients receiving typical antipsychotics and 21% of those receiving atypical antipsychotic medication remained in treatment after six months [15]. Other authors have also substantiated the poor rates of treatment persistence among patients with schizophrenia in Africa, Asia, Europe and North America [16,17].

In the current study, there was no significant difference in treatment persistence between patients receiving typical and atypical antipsychotics. Previous research yielded contrasting findings regarding the association between class of antipsychotics and persistence in treatment. While some authors reported that patients receiving atypical antipsychotics were more likely to persist in treatment than patients receiving typical antipsychotic medications [14,17,37,38] others found no association between treatment persistence and class of antipsychotics [28-29,34,39-40].

It has been argued that the seemingly lower persistence rates associated with typical antipsychotics in clinical trials is attributable to comparatively higher doses of typicals commonly used in these studies, with consequent intolerable extra-pyramidal adverse effects such as acute dystonia, oculo-gryic crises, excessive salivation, and tongue protrusion [41,42]. A meta-analysis of several studies attributed the variance in treatment persistence between patients receiving typical and atypical antipsychotics to disparity in dose of antipsychotics rather than differences between classes of antipsychotics [41]. However, a naturalistic study where patients received comparatively moderate dose of first-generation antipsychotics and another meta-analytic research reported divergent findings [14,43]. Furthermore, the mandatory monitoring of granulocyte count required of patients treated with clozapine in order to avert potentially fatal adverse effects, may contribute to a higher persistence rate attributed to atypical antipsychotics [44].

The low rate of treatment persistence in this study is a grave finding considering the known negative consequences of untreated schizophrenia [2,6-10]. Drop-out from treatment significantly increases the risk of relapse, re-hospitalisation, poor quality of life and suicide among patients with schizophrenia [2,6-10]. In light of this evidence, there is a dire need for interventions to facilitate persistence in treatment among patients with schizophrenia. Clinicians need to recognise that the lesser propensity for extra-pyramidal side effects associated with the use of atypical antipsychotics does not guarantee persistence in treatment. Efforts must be intensified to educate patients and their family members on the chronic nature of schizophrenia, the benefits of treatment persistence and the consequences of treatment discontinuation. Policy makers also need to address potential systemic barriers to treatment persistence including poor mental health care financing, non-integration of mental health into primary care,
stigma, and poor access to mental health services [30,45,46].

The retrospective design of the current study limits insight into the specific experiences of service users which could have contributed to lack of persistence in treatment. Secondly, documentation errors and missing records may distort the results. Furthermore, patients reckoned to have dropped out of treatment may have relocated to another mental health facility to obtain treatment since most facilities in Nigeria are open to patients who walk-in without formal referrals. The major strength of this study is its naturalistic design which precludes the influence of the researcher or any other form of inducement that could preferentially facilitate treatment persistence in any of the study groups. Secondly, a standardised approach, consistent with previous research, was used to estimate treatment persistence in order to facilitate comparison across studies. Furthermore, the study has provided valuable information on a previously under-researched subject in Africa.

5. CONCLUSION

The current study demonstrated a very poor rate of persistence in treatment among patients with schizophrenia after discharge from the hospital. There was no significant difference in treatment persistence between patients receiving typical and atypical antipsychotics. This is a grave finding considering the negative consequences of non-persistence in treatment including increased risk of relapse, re-hospitalisation and suicide. There is an urgent need for interventions to facilitate treatment persistence among patients with schizophrenia.

CONSENT AND ETHICAL APPROVAL

Consent is not applicable because this study is a retrospective chart review and not a case report. Ethical approval was obtained from the Research and Ethical Committee of the institution.

ACKNOWLEDGEMENT

Dr Maitanmi, Dr Fadahunsi and Dr Pedro assisted in extraction of clinical records, while Dr Adegbohun contributed to data input.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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