Are depot anti-psychotics associated with longer persistence in treatment compared with oral antipsychotics among patients with Schizophrenia?

ABSTRACT

Aim: Non-adherence with antipsychotics is associated with poor outcomes in patients with schizophrenia. It was anticipated that drop-out from treatment due to non-compliance with oral anti-psychotics could be abated with the use of depot antipsychotics. However previous studies are divergent regarding the association between persistence in treatment and the use of depot antipsychotics. This study aimed to compare treatment persistence among out-patients with schizophrenia receiving depot versus oral antipsychotics in Lagos, Nigeria.

Methodology: Relevant clinical data of out-patients with schizophrenia (n=160) were retrieved one year post-hospitalisation at a public psychiatric facility in Nigeria. Treatment persistence (time to all cause treatment discontinuation) among the cohort of patients was determined using the Kaplan-Meier Survival analyses. Persistence in treatment between patients receiving depot versus oral antipsychotic medications alone was compared using the log rank test.

Results: Nearly half (49.1%) of the cohort dropped out of treatment within one month of discharge, while 18.2% persisted for one year. There was no significant difference (p=0.727) in the mean duration of treatment persistence between patients receiving depot antipsychotics (17.4(±2.4) weeks), and those receiving oral medications alone (19.4 (±2.2) weeks).

Conclusion: There is a high rate of drop-out from treatment among patients with schizophrenia, after discharge from in-patient care. Prescription of depot medications was not associated with longer persistence treatment in the studied cohort. This finding highlights the need to develop interventions to facilitate treatment persistence among patients with schizophrenia.

1. INTRODUCTION

Schizophrenia is a severe disorder that interferes with functioning in multiple neuro-psychological domains including cognition, perception, and thought systems. Schizophrenia usually runs a chronic course which may be punctuated by intermittent periods of remission and relapse. Anti-psychotics are the mainstay in the treatment of schizophrenia, and are effective in the treatment of psychotic symptoms, as well as reducing the risk of relapse and re-hospitalisation [1, 2].

Despite the availability and effectiveness of anti-psychotics in the therapy of schizophrenia, research has consistently shown a low rate of treatment adherence or persistence in treatment. More than half of patients with schizophrenia discontinue anti-psychotics treatment within the first year of onset of treatment [3-5]. Non-persistence in treatment has dire clinical, social and public health implications including increased risk of relapse, re-hospitalisation, increased burden on emergency services, suicide and mortality [6-10].

In terms of efficacy in the treatment of the positive and negative symptoms of schizophrenia, evidence has shown that depot antipsychotics are at least at par with their oral equivalent, if not better [11-17]. In addition, depot formulations are expected to address non-compliance attributable to forgetting to use medications or lack of insight; which are quite common among patients with schizophrenia [15-17]. On the flip side, pain at injection sites, perception of coercion or lack of autonomy and stigma may not favour adherence with depot anti-psychotics [15-17].

With the advent of long acting injections, it was envisaged that these medications would facilitate monitoring of treatment compliance, thereby guaranteeing administration of medications and transparency of adherence [15-17]. Consequently, it was anticipated that this would allow the clinicians to be promptly alerted and intervention instituted if patients fail to receive their depot medications. The anticipation that depot antipsychotics would guarantee treatment adherence and persistence in treatment has not been consistently substantiated by extant research evidence. While several authors reported a longer persistence in treatment or better adherence with depot versus oral antipsychotics in naturalistic samples, results of randomised control trials and meta-analyses contradict these findings [15-22].

A few studies have reported high rates of non-compliance with medications or clinic appointments among patients with chronic psychiatric disorders in sub-saharan Africa [23-28]. However, there is dearth of evidence on treatment adherence or treatment persistence with depot versus oral anti-psychotics in Africa. A retrospective study conducted at a tertiary mental health service in Nigeria found that less than a quarter of patients with schizophrenia persisted in treatment for one year [27]. A more recent study conducted at a psychiatric hospital in south-west Nigeria reported similar findings [28]. However, these studies did not investigate the relationship between route of administration of medications and treatment persistence. The current study aimed to compare persistence in treatment between patients with schizophrenia receiving depot antipsychotics and those receiving oral antipsychotics after discharge from in-patient care to out-patient clinic in a Nigerian psychiatric hospital.

METHODOLOGY

The methodology of the current study has been previously described by the author in a recent study comparing treatment persistence among patients with schizophrenia receiving first-generation versus second generation oral antipsychotics [28]. The study was conducted at a public tertiary mental health care facility, Federal Neuro-Psychiatric Hospital Yaba Lagos, located in south-West Nigeria. The hospital has an in-patient facility with 500 beds and out-patient clinics attended by more than a thousand patients weekly. The study design was a retrospective cohort study.

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 constituted the study population. As part of a larger study of clinical outcomes in patients with schizophrenia, the medical records were reviewed between October and December 2013 to assess 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 [29]. Patients less than 18 years and greater than 65 years were excluded from the sample.

Data retrieved for each patient included socio-demographic characteristics, clinical diagnosis, number of episodes of illness, number of psychiatric hospitalisations, prescribed class and route of administration of anti-psychotic medications (e.g. typical or atypical and depot versus oral), and attendance of out-patient clinic appointment/prescription refill over a period of one year after discharge from the hospital (treatment persistence).

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. Similar definition has been used by previous researchers on this subject [4, 30]. Treatment gap commenced from the date of the missed clinic appointment/ prescription refill. Research indicates that medical records of clinic attendance/prescription refill highly correlate with pharmacy refill and these indices are valid indirect measures of treatment adherence [4, 31-32].

Routinely, the standard protocol at the facility where the study was conducted is such 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. All the patients on depot medications were on typical (first-generation) depot antipsychotics such as fluphenazine, depixol and clopixol in addition to oral antipsychotics. The oral antipsychotics regularly available in the hospital at the time of the study included olanzapine, risperidone, clozapine, chlorpromazine, trifluoperazine and haloperidol. Institutional approval was obtained from the Research and Ethical Committee.

Statistical Analysis: Data was analysed with IBM- SPSS (version 20). Kaplan-Meier Survival analyses was used to determine the major outcome of interest; persistence in treatment. 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 depot versus oral antipsychotics.

2. RESULTS

The current sample consisted of 160 patients with schizophrenia discharged from in-patient to out-patient clinic at a public psychiatric Hospital in Nigeria. There were more females (59.4%) than males, and less than one third (31.3%) were married. The mean age of the patients was 38.7 (±11.4) years (Table 1). The majority attained secondary (35%) or tertiary (43%) levels of education, but only 36.5% were employed. Among the cohort that constituted the study sample, the median number of episodes of schizophrenia was 2, while the median number of psychiatric hospitalisation was 1. Depot antipsychotics were prescribed for 48.1% of the patients, while 51.9% received oral antipsychotics alone.

Table 1: Socio-demographic characteristics of the patients in the sample

	N= 160	
Variable	n	(%)
Gender		
Male	65	(40.6)
Female	95	(59.4)
Marital status		
Married	50	(31.3)
Single	110	(68.7)
Employment status		
Employed	58	(36.5)
Unemployed	102	(63.5)
Level of education		
No formal education	5	(3.1)
Primary	18	(11.3)
Secondary	56	(35.0)
Tertiary	69	(43.1)

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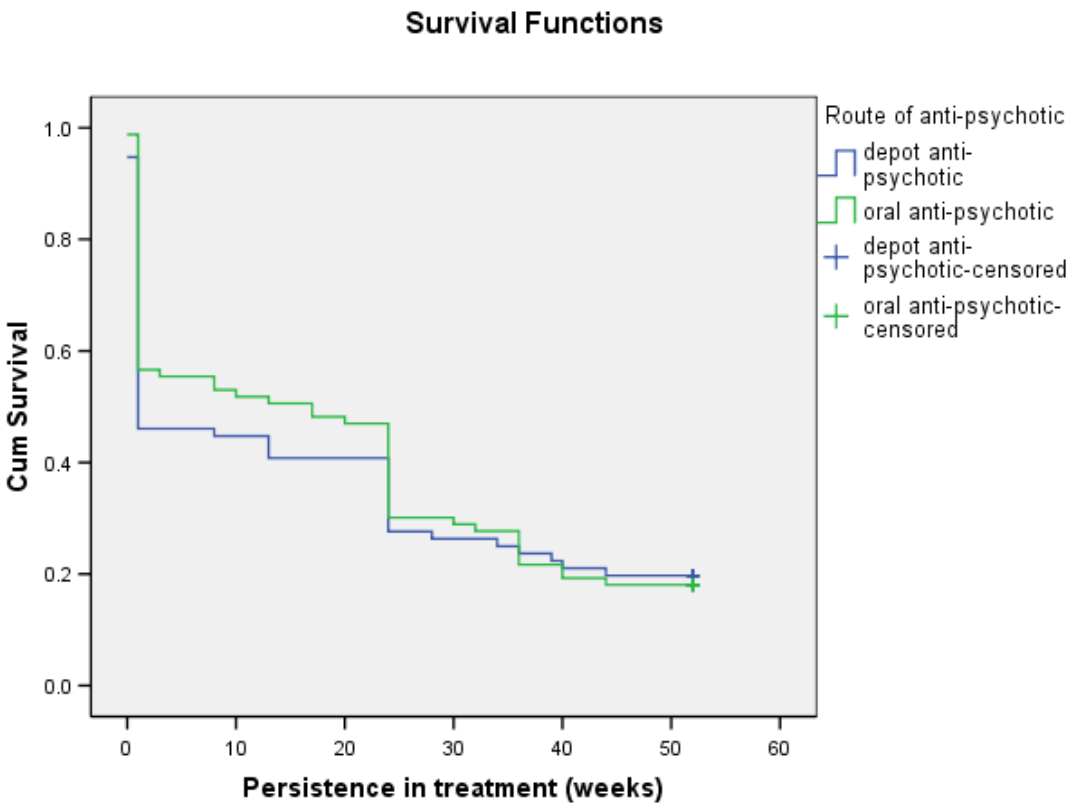
Based on the earlier defined criteria, only 50.9% of patients with schizophrenia persisted in treatment one month after discharge from the hospital. Subsequently, there was a gradual decline in persistence in treatment. By the end of the third and sixth month, 45.9% and 28.9% of the patients persisted in treatment respectively. Only 18.2% had not defaulted from treatment one year after discharge from the hospital.

The mean time to all cause treatment discontinuation calculated by the Kaplan-Meier survival analysis (figure 1) indicated that the mean duration of treatment persistence among the patients was 18.5 (±1.6) weeks (95% C.I= 15.4-21.6). Among patients receiving depot antipsychotics, the mean duration of treatment persistence was 17.4(±2.4) weeks (95% C.I= 12.8-22.1), while those receiving oral medications alone had mean duration of treatment persistence of 19.4 (±2.2) weeks (95% C.I= 15.2-23.7). Using the log-rank (Mantel-cox) test, a comparison of the survival times between both groups of patients revealed no statistically significant difference in treatment persistence (chi-square=0.122, p=0.727).

Figure1: Kapan-Meier survival analysis curve comparing treatment persistence between patients using depot versus oral antipsychotics



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156 ## 3. DISCUSSION

157 This study compared persistence in treatment between out-patients with schizophrenia receiving
158 depot antipsychotic medications versus those receiving oral antipsychotics alone, following discharge
159 from a tertiary psychiatric care facility in south-west Nigeria. The socio-economic profile of the patients
160 in this cohort is consistent with the pattern of impairment in social and occupational domains typically
161 seen in patients with schizophrenia [33].

162 Within one month of discharge from in-patient care, nearly half of the sample had dropped out of
163 treatment, and by the end of the third month post-discharge, only 46% persisted in treatment. A study
164 of post-discharge treatment adherence among patients discharged from a Psychiatric Hospital in
165 Nigeria similarly reported that only 50.6% of the patients were persistent in treatment until the 3rd
166 month post-hospitalisation [24]. The current study also found that about 4 out of 5 patients with

schizophrenia had dropped out of treatment within one year of discharge to out-patient care. This finding is consistent with that reported among patients with first episode schizophrenia in south-west Nigeria, where only 1 out of 4 patients persisted in treatment for one year [27]. Research evidence from other parts of the globe including North America, Europe and Asia have also demonstrated low rates of persistence in treatment among patients with schizophrenia [4, 5, 34-38].

The current study found no significant difference in treatment persistence between patients receiving depot and oral antipsychotics. Previous research on this subject demonstrated divergent findings. While some authors reported that patients with schizophrenia or first episode psychosis treated with depot antipsychotics had significantly longer time to discontinuation of treatment compared to patients on oral antipsychotics [15, 17, 39-43] others found no association between treatment persistence and route of administration of antipsychotics [15,17-22]. The largest meta-analysis of randomised controlled trial on this subject comparing depot versus oral medication among patients with schizophrenia found no significant difference [16, 22]. It was envisaged that long acting injections would facilitate monitoring of treatment compliance, thereby guaranteeing administration of medications and transparency of adherence [16]. Consequently, it was anticipated that this would allow the clinicians to be promptly alerted and intervention instituted if patients fail to receive their depot medications.

In the current study, patients who received depot medication prescriptions had shorter persistence in treatment compared with patients receiving oral antipsychotics alone. Studies have shown that patients may perceive long acting anti-psychotic injections as coercive and stigmatizing, and such attitudes could consequently lead to non-adherence [44]. Furthermore, the injections are associated with tissue irritation and pain which may discourage persistent compliance. The low rate of treatment persistence among patients receiving depot antipsychotics may also be attributed to the fact that patients selected by clinicians to receive depot medication prescription in the first place may be patients perceived by clinicians to have high risk of drop-out from treatment. Evidence indicates that clinicians are more likely to prescribe depot form of medications to patients with past history of poor adherence with oral medications and those with a past history of relapse [16, 45]. On the other hand, patients with high level of insight and good therapeutic alliance are more likely to receive prescriptions of oral medications than long acting injections.

The high rate of drop-out from treatment, even among patients who received long acting anti-psychotic injection prescription is a worrisome finding because of the associated increased risk of relapse, re-hospitalisation and burden of treatment [6-10]. This is particularly important in a low-resourced country where community based mental health resources are scarce, and prescription of long-acting injections to patients perceived to have a high risk of default may be one of the few or perhaps the only feasible 'intervention' relied on to facilitate persistence in treatment. This finding highlights the need for other interventions to facilitate persistence in treatment among patients with schizophrenia. Patients with schizophrenia and their informal caregivers must be educated on the chronic nature of the disease and the consequences of discontinuation of treatment. Furthermore, advocacy efforts must be stepped up in order to ensure that barriers to treatment persistence such as poor access to mental health services, poor mental health care financing, non-integration of mental health into primary care and stigma are addressed by policy makers [23, 46, 47].

In comparing this study with previous research on this subject, it is important to note that the patients receiving depot medications were also using oral anti-psychotics concomitantly. The current study is limited by its retrospective design which precludes face to face interview with service users and consequently information on the specific barriers to persistence in treatment. Furthermore, since most mental health facilities in Nigeria accept patients without formal referrals, patients who appear to have dropped out of treatment may have opted to continue treatment in another facility without documentation. Finally data retrieved from health records may be limited by missing data and errors of documentation. The major strength of the current study lies in the standardised approach used to estimate treatment persistence, in consistence with previous research. Furthermore, the naturalistic design of the study which bars the influence of the researcher, or any other form of inducement that could preferentially facilitate treatment persistence in any of the study groups also adds to the strength of the study.

CONCLUSION

The current study found a high rate of drop-out from out-patient treatment among patients with schizophrenia post-hospitalisation. There was no significant difference in persistence in treatment between patients receiving long acting anti-psychotics injections and those receiving only oral

antipsychotics. These findings highlight the need for interventions to minimise drop-out from treatment among patients with schizophrenia.

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