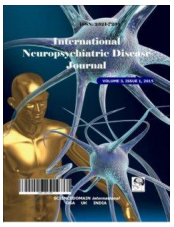

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Efficacy and Tolerability of Aripiprazole in a Nigerian Cohort with First-episode Psychosis: A Post-marketing Survey

S. O. Olotu[1*], I. O. Agbonile[1], J. O. Omoaregba[1] and B. O. James[1]

[1]Department of Clinical Services, Federal Neuropsychiatric Hospital, Benin-City, Nigeria.

Authors' contributions

This work was carried out in collaboration between all authors. All authors designed the study, while authors SOO and BOJ wrote the protocol. All authors wrote the first draft of the manuscript. Author BOJ managed the analyses of the study. Authors IOA and JOO managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Individuals with first episode psychoses often discontinue pharmacotherapy due to poor symptom remission and/or intolerable side effects. Aripiprazole has been reported to show good efficacy with low side effect profiles in Caucasians. No studies have been conducted to assess its effectiveness and tolerability in a Nigerian population hence the need for this study.
Methods: A post marketing surveillance was conducted involving patients with first episode psychosis presenting to a regional tertiary psychiatric facility in Nigeria. Participants were titrated through a dose range of 10-30 mg of aripiprazole depending on response or tolerability and followed up over a 12 week period. Assessments at baseline, at 2, 6, and 12-weeks post recruitment were done to rate severity of psychopathology (CGI, PANSS), side effects (MSAS), functioning (GAF), and medication adherence (MARS).
Results: Of fifty patients completing the study (49.5% drop-out rate), we observed significant improvements at 12 weeks compared to baseline in symptom remission ($p<0.001$), clinician rating of improvement ($p<0.01$), and psychosocial functioning ($p<0.001$). There were no significant

**Corresponding author: E-mail: osolotu@yahoo.com;*

changes compared to baseline as regards medication adherence, extra pyramidal side effects (p=0.23), fasting blood sugar (p=0.67) and fasting cholesterol (p=0.57)
Conclusion: Aripiprazole may be effective and tolerable among individuals with first episode non-affective psychoses presenting at a tertiary psychiatric facility in Nigeria.

Keywords: Aripiprazole; first episode psychoses; tolerability; efficacy; Nigeria.

1. INTRODUCTION

Individuals with first-episode psychosis (FEP) may go on to develop schizophrenia; arguably one of the most costly mental illness in terms of its huge, wide ranged and long lasting economic impact on individuals, families and communities [1]. While none or poor adherence to medications is common among individuals with FEP, antipsychotic medications remain the mainstay of management.

Aripiprazole, is an antipsychotic which was first used as pharmacotherapy for psychotic disorders in the USA in 2002. A starting and maintenance dose of 10-15 mg/day is recommended [2]. Its effective dose range is from 10 to 30 mg, and it can be administered once daily. Aripiprazole can be administered at any time of the day and can be taken with or without meals. Its unique mechanism of action differentiates it from all other available antipsychotic medications. Aripiprazole acts as an antagonist at serotonin 5-HT2A receptors, while at 5-HT1A and dopamine D2 receptors, it acts as a partial agonist [3–5]. Kikuchi et al. [6], found that in an animal model, aripiprazole tends to act as an agonist in regions of low dopamine transmission, while in regions of dopamine over activity, it tends to reduce dopamine transmissions of dopamine.

The molecule has varying affinity for multiple receptors: it has high affinity dopamine D2 and D3 receptors as well as to serotonin 5-HT1A and 5-HT2A receptors, while it has low affinity for other receptors such as dopamine D4, serotonin 5-HT2C and 5-HT7 receptors, a1-adrenergic and to H1 receptors. It binds only loosely to muscarinic receptors [7]. Aripiprazole has been proven to be safe and easily tolerable in patients with schizophrenia. Several controlled clinical trials [8] have revealed that the efficacy is high and that positive and negative symptoms of schizophrenia were significantly improved with the administration of aripiprazole.

Some premarketing aripiprazole studies have also been conducted; such as the BETA (Broad Effectiveness Trial with Aripiprazole) trial in the USA [9] & Europe [10] and the STAR (Schizophrenia Trial of Aripiprazole) trial in Europe. These trials concluded that aripiprazole was well tolerated in patients with schizophrenia, that it effectively reduce symptoms of schizophrenia, and that it improves the quality of life of outpatients and inpatients with schizophrenia.

A post marketing surveillance of aripiprazole was done in 2004 in Germany [11]. It was a multicentre, prospective cohort study which was sponsored by the manufacturers of aripiprazole (ABILIFY), Bristol- Myers Squibb and Otsuka Pharmaceutical. It was observed that over the 4 weeks study period Aripiprazole was well tolerated and that there was significant improvements in the ratings of the CGI, GAF, and SF-12. Observed adverse effects were mild to moderate and were mostly nausea, vomiting, insomnia, irritability and restlessness. They concluded that Aripiprazole, over a 4 week period can significantly improve schizophrenia symptoms in inpatients as well as outpatients.

Aripiprazole has not been formally licensed for use in Nigeria for the treatment of schizophrenia. There is a need to generate data and evidence among patients in Nigeria with a view to its introduction as a pharmacological treatment option. It has been argued that genetic differences influence pharmacokinetic and pharmacodynamic actions of antipsychotics [12]. The present study is a post marketing surveillance study which seeks to investigate the efficacy, tolerability and safety of Aripiprazole among in- and out-patients with a first episode of a non-affective psychosis in a regional tertiary psychiatric facility in Nigeria.

2. METHODS

2.1 Setting

This post-marketing survey was conducted at the Federal Neuro-Psychiatric Hospital (FNPH), Benin-City, Nigeria between June 2015 and January 2016. The FNPH, Benin-City is one of eight mono-specialist tertiary psychiatric facilities in Nigeria and provides referral and walk-in

psychiatric care on in- and out-patient basis to individuals across all age spectrums with varied psychiatric diagnoses. Cases are derived primarily from its catchment area of Edo, Delta, and Ondo states, but it also receives a significant proportion of cases from all states of the federation.

2.2 Participants

Individuals with a first episode of a psychotic disorder (FEP) were recruited into the study, if they were between the ages of 18 and 64 years. FEP was operationalised for this study as having an episode of symptoms comprising hallucinations, delusions or disorganised behaviour lasts in excess of 1 week (or less if severe enough to disrupt psychosocial functioning). To be classified as FEP individuals were having a first episode. To be included in the study, participants had to understand the nature and purpose of the study, and provide written informed consent (patient/caregiver). Patients with FEP were excluded from the study if they had been on antipsychotic medications in the 6 months preceding recruitment, had a co-existing endocrine disorder e.g. diabetes or had identifiable logistic constraints that would clearly impede accurate follow-up.

2.3 Procedure

A convenience sample of 101 participants who satisfied the inclusion criteria were recruited into the study. Each participant (and/or caregiver, where applicable), had the study protocol explained and written informed consent obtained.

Each participant then received an assessment at baseline (week 0) which included socio-demographic details, confirmation of psychosis using the Psychosis module of the Mini International Neuropsychiatric Interview (MINI). Severity of symptoms was rated using the Positive and Negative Syndrome Scale (PANSS) and the Clinician Global Impression Scale (CGI). Functioning was assessed using the Global Assessment of Functioning Scale (GAF) and presence of any side effects at baseline using the modified Simpson Angus Scale (MSAS). All participants at baseline also had height/weight measures, and the following investigations; electrocardiogram (ECG), fasting blood sugar (FBS), full blood count (FBC), fasting lipid profile (FLP) and urinalysis done.

Participants were followed up over a 12 week period. Three other assessments from baseline were undertaken at weeks 2, 6 and 12. At weeks 2 and 6, participants had a standard clinical review and were administered the PANSS, CGI, MSAS, Medication Adherence Rating Scale (MARS) and the GAF. At week 12, in addition to the assessments conducted at weeks 2 and 6, participants had the following investigations (FBS, FLP, FBC, ECG and urinalysis).

All participants received a range of medications at the discretion of the clinician throughout the period of follow-up. The only atypical antipsychotic administered was aripiprazole. Clinicians were free to discontinue treatment with aripiprazole following duration of poor treatment response or complaints of intolerable side effects. Aripiprazole was administered at doses of 10-30 mg based on symptom severity or clinical response.

2.4 Instruments

2.4.1 Socio-demographic questionnaire

This questionnaire was designed by the investigators and captured relevant variables like age, gender, ethnic group, religion, and body mass index (BMI).

2.4.2 Mini international neuropsychiatric interview (MINI)

The Mini-international neuropsychiatric interview is a short structured clinical interview which enables researchers to make diagnoses of psychiatric disorders according to DSM-IV or ICD-10 [13]. The administration time of the interview is approximately 15 minutes and was designed for epidemiological studies and multi-centre clinical trials. The MINI-International Neuropsychiatric Interview (MINI(-Plus)) is designed to provide reliable diagnosis in less time than other diagnostic interviews such as the Structured Clinical Interview for DSM-IV disorders (SCID), the Composite International Diagnostic Interview (CIDI) or the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) with comparable psychometric characteristics. The psychosis module was used in this study.

2.4.3 Positive and negative syndrome scale (PANSS)

The Positive and Negative Syndrome Scale (PANSS) provides for a typological and dimensional assessment of symptoms in psychotic illnesses in general and schizophrenia

in particular. The 30-item PANSS was conceived as an operationalized, drug-sensitive instrument that provides balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology. It thus constitutes four scales measuring positive and negative syndromes, their differential, and general severity of illness [14]. It has good internal consistency, concurrent validity and discriminant validity between its positive and negative subscales [15].

2.4.4 Clinical global impression scale (CGI)

The Clinical Global Impression (CGI) rating scales are commonly used measures of symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders [16]. 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, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1; normal, through 7; extremely ill. The Clinical Global Impression – Improvement scale (CGI-I) is a 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention and rated from: 1, very much improved through 7, very much worse. The Clinical Global Impression – Efficacy Index is a 4 point rating scale which assesses the therapeutic effect of the treatment as 1, unchanged to worse; 2, minimal; 3, moderate; 4, marked.

2.4.5 Global assessment of functioning scale (GAF)

The Global Assessment of Functioning (GAF) is a numeric scale (1 through 100) used by mental health clinicians and physicians to rate subjectively the social, occupational, and psychological functioning of adults. It describes how well an individual is functioning within the context of an illness. Rating ranges from 1-10 (Persistent danger of severely hurting self or others e.g., recurrent violence *or* persistent inability to maintain minimal personal hygiene *or* serious suicidal act with clear expectation of death) and 91-100 (No symptoms. Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities). Higher scores ranges indicate better functioning.

2.4.6 Medication adherence rating scale (MARS)

The medication adherence rating scale (MARS) is a 10-item self-report questionnaire that has utility in the assessment of adherence to antipsychotic treatment. It was developed to overcome limitations to the Drug Attitude Inventory (DAI) [17]. A recent validation study has shown that the MARS has moderate to strong internal consistency and weak to moderate concurrent validity [18]. Scores are rated from 0 to 10, with higher scores indicating better adherence.

2.4.7 Modified simpson angus scale (MSAS)

The modified Simpson-Angus Scale (MSAS) is a 10-item rating scale used widely in the screening and assessment of antipsychotic induced park insonism in both clinical practice and research settings. It consists of one item measuring gait (hypokinesia), six items measuring rigidity and three items measuring glabella tap, tremor and salivation, respectively. It has been shown to exhibit good reliability (Cronbach alpha=0.97) and discriminant validity [19,20].

2.5 Outcome

The primary outcome (mean reduction in PANSS scores over 12 weeks from baseline) was set a-priori. Secondary outcomes of interest was mean increase in functioning, and no significant increase in side effects profile at 12 weeks compared to baseline.

2.6 Ethical Considerations

The study protocol was approved by the Ethics Committee of the Federal Neuro-Psychiatric Hospital, Benin-City. All participants/ caregivers were informed about the nature of the study and provided written informed consent.

2.7 Data Analysis and Management

Data was entered into an electronic spreadsheet and analysed using the statistical software; SPSS v.20. Descriptive statistics was used to summarise the data and presented in tables,

charts and graphs. Comparisons between patient ratings at baseline and at 12 weeks were performed using the paired t-tests. Level of significance was set at $p<0.05$

3. RESULTS

3.1 Study Participant Flow

A total of 101 individuals were recruited into the study between June and December, 2015. Fifty persons completed the study (49.5% completion rate). Sixteen (15.8%) dropped out after baseline assessment. Reasons for discontinuation included improvement in symptoms (n=9), and logistic challenges (n=7). Twenty-two (37.6%) dropped out after the first follow-up at the 2nd week post recruitment, of which one sought alternative care due to worsening symptoms and the others cited the logistic constraint of commuting to the treatment centre, 12 (11.9%) dropped out after the second follow-up visit at week 6. Two due to insomnia and the others said their symptoms had improved and required no follow-up care. One (1.0%) was withdrawn from the study after week 10 due to intolerable extra pyramidal side effects.

The outcome measures of interest reported is from the analysis of the 50 participants who completed the study

3.2 Socio-demographic Characteristics of Participants

The mean age (SD) of participants was 33.3 (12.5) years. Female participants (35.9 years) were significantly older than their male (30.0 years) counterparts (t=2.45, df=99, p<0.02). There was a preponderance of females (n=55, 54.5%). Over half had at least up to some secondary level of education (66.0%). The majority were Christian (97.0%) with the modal ethnic grouping being Benin (n=28, 27.7%). Over two-thirds were single (n=68, 67.3%), and unemployed (n=69, 68.3%).

3.3 Clinical Characteristics of Participants

All participants' diagnoses were confirmed using the MINI as having a current episode of a DSM-IV psychotic disorder without affective symptoms. A majority (n=83, 82.2%) were having a first episode of a psychotic illness, similarly most (n=79, 78.2%) had not received any antipsychotic medication prior to recruitment into the study.

3.4 Comparison of Socio-demographic and Clinical Characteristics of Study 'Completers' and 'Non-completers'

Participants who completed the study were on average younger; 32.4 (13.7) years, when compared to 'non-completers'; 34.1 (11.2) years, though this difference was not statistically significant (t=0.67, p=0.51). Both groups did not differ regarding any other socio-demographic or clinical characteristic assessed at baseline; level of education (p=0.78), gender (p=0.27), religion (p=1.00), ethnic group (p=0.41), marital status (p=0.56), employment status (p=0.83), episode of illness (p=0.11) or prior use of antipsychotics (p=0.59)

Baseline assessments of severity of psychopathology, functioning and baseline EPSE were similar across both groups. PANSS positive (p=0.11), PANSS negative (p=0.23), PANSS general (p=0.69), GAF (p=0.45), MSAS (p=0.17). These suggest that the power of the study findings are not diminished by the rate of non-completion observed.

3.5 Clinical Outcome (PANSS) for Study 'Completers' (n=50)

Treatment effectiveness was ascertained using scores on the total PANSS scores and domains at baseline and at pre-determined follow-up points. On total score and all domains there was a significant reduction in symptom scores from baseline; total (t=122.74, df=47, p<0.001), positive (t=13.29, df=47, p<0.001), negative (t=4.28, df=47, p<0.001), general (t=11.10, df=47, p<0.001). Marked reduction in symptom profile was observed as early as the second week, with a further drop by the 6th week. No significant changes were observed between the 6th and 12th weeks of assessment. See Fig. 1.

3.6 Outcomes of CGI Ratings

A similar trend was seen regarding clinician rating of illness severity from baseline, as well as ratings of global improvement and efficacy from week 2. There was a significant improvement in clinician rating of illness severity from baseline (p<0.01), global improvement (p<0.02) and efficacy (p<0.001). See Fig. 2.

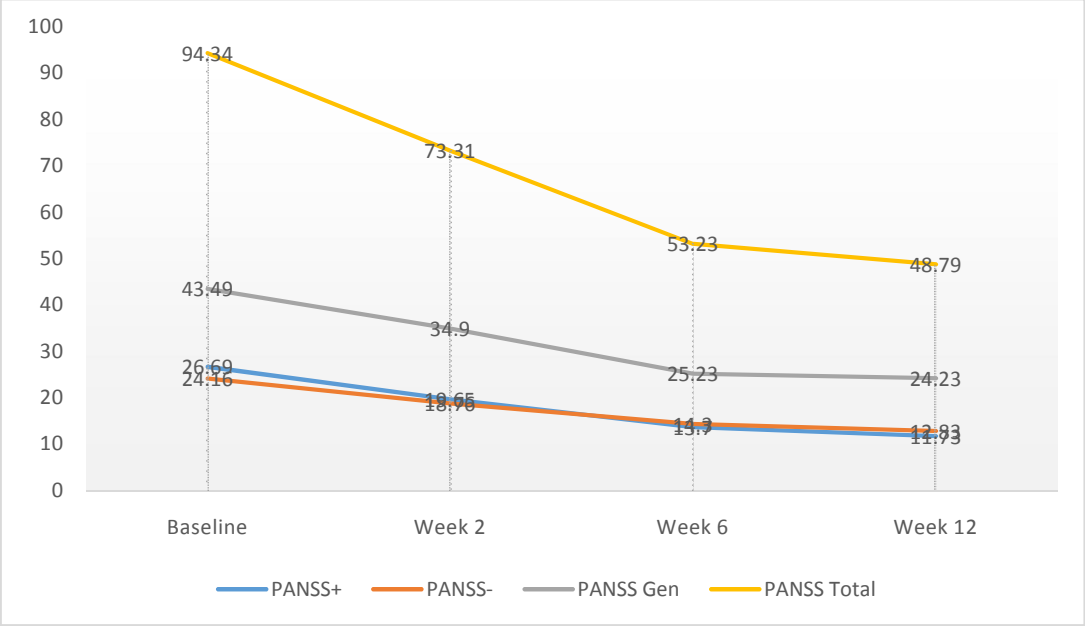

Fig. 1. Trend in reduction in average PANSS total domain scores and in the positive, negative and general subscales

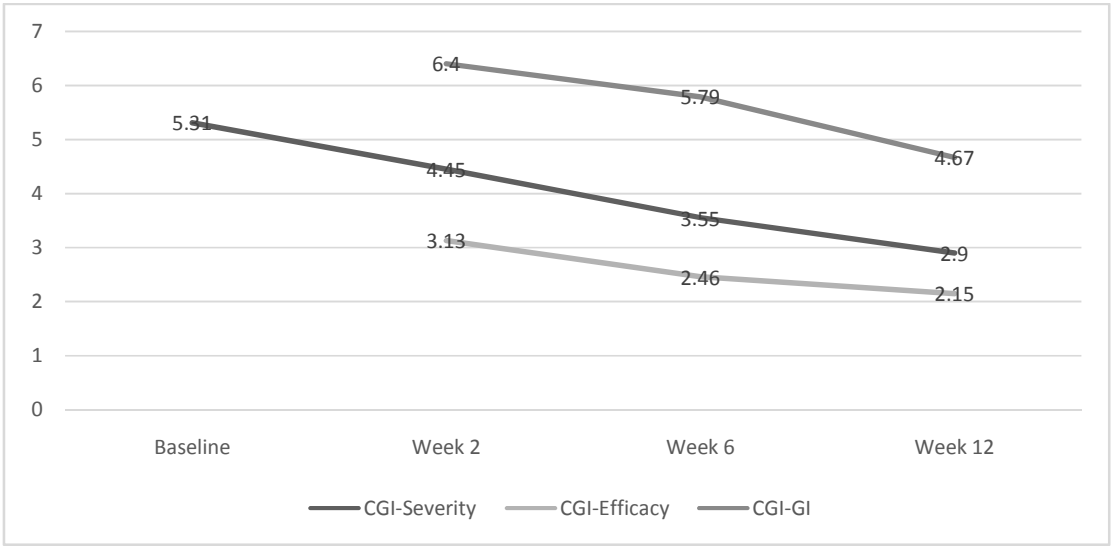

Fig. 2. Clinician rating of illness severity, global improvement and drug treatment effect

3.7 Functioning and Tolerability

Reduction in severity of symptoms was also associated with improvement in psychosocial functioning at week 12 compared to baseline (p<0.001). There was no significant change in EPSE side effect profile at 12 weeks compared to baseline (p=0.23), similarly adherence measures were consistent between weeks 2 and 12. See Fig. 3.

There was no significant change in fasting blood sugar and cholesterol levels at week12 compared to baseline. FBS (baseline: 91.46 vs. week12: 89.85; t=0.43, p=0.67). Fasting cholesterol (baseline: 136.4 vs. week 12: 140.97; t=-0.57, p=0.57).

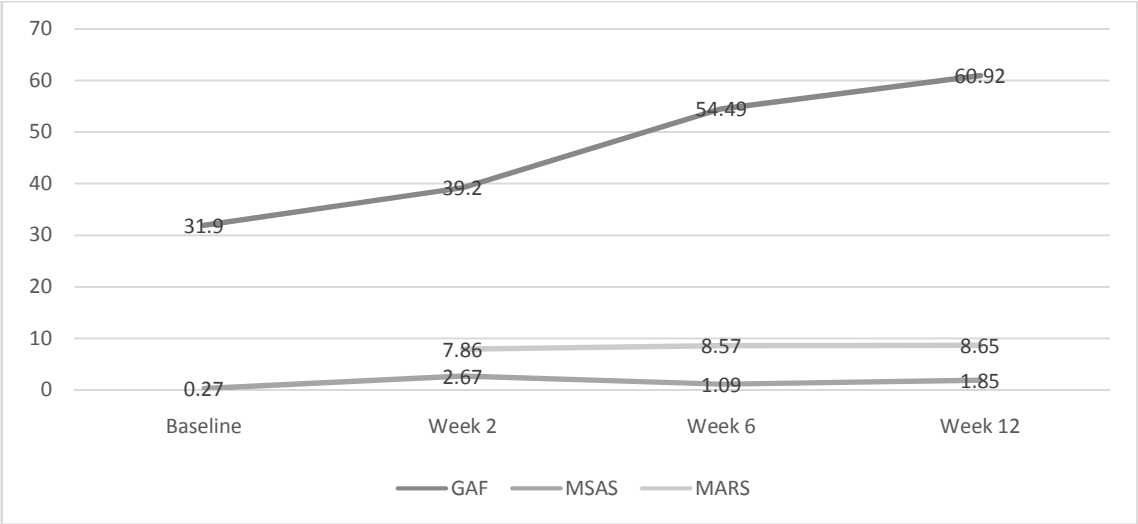

Fig. 3. Trend in functioning, EPSE profile and medication adherence

4. DISCUSSION

This post marketing survey ascertained the efficacy and tolerability of aripiprazole in the treatment of first episode psychotic disorders. We found that aripiprazole use was associated with reduction in symptom severity profile on the PANSS and improvement in subjective clinician rated assessment on the CGI. Additionally, we found that aripiprazole was tolerated with no change in side effect ratings at 12 weeks compared to baseline.

Our efficacy data demonstrated a rapid onset of treatment effectiveness and significant reduction in symptom severity on both PANSS and CGI measures from the 2nd week to the 6th week. This finding is consistent with reports from previous short term studies on the efficacy of aripiprazole like the BETA study [9,21,22]. The efficacy measures however did not differ between the 6th and the 12th week indicating that there was no further improvement achieved in symptom severity between the 6th week and 12th week. Due to the short period of observation, it cannot be inferred that patients would not improve further over time and future studies over longer observation periods are desirable.

The goal of therapy often includes restoration of adequate psychosocial functioning which is usually disrupted by psychotic disorders. Adherence to medication is considered a key factor in achieving restoration of psychosocial functioning as well as attenuation of symptoms of the disorder. There was a significant improvement in the psychosocial functioning as measured by GAF within the period of observation among participants of the trial. The marked improvement was noticeable as early as the second week of commencement of aripiprazole therapy and continued till the endpoint at 12 weeks. In contrast, the adherence measures did not differ at endpoint compared to baseline which suggests that the drug was well tolerated especially when considered against the background of the findings of improved psychosocial functioning, low EPSE profile and absence of adverse effects on blood sugar and cholesterol levels.

Within the period of observation, there was a relatively high dropout rate of 50.5%, this is consistent with reports from a previous study done in the USA [21]. They reported in 2003 a drop-out rate of 37% over 4 weeks, this dropout rate was in spite of a concomitant finding of low adverse side effects compared to placebo [21]. In contrast, a study from India [23]. reported a low dropout rate of 7% with mild to moderate adverse effects reported, the dropout rate was however consistent with the finding of low rates of reported adverse effects.

Interestingly, in the current study, as in the study by Potkin et al. [21] dropout rates did not seem to be consistent with the experience of side effects. Other studies have also documented relatively high discontinuation rates against a background of good tolerability and low rates of reported side effects [21,24,25]. A more weighty argument for this inconsistency seems to be suggested by the

finding of Potkin et al. [21] that the discontinuation rate for placebo (50%) was higher than that for Aripiprazole (37%). Perhaps this lends credence to the argument that discontinuation may not be as a result of adverse effects inherent in the use of aripiprazole in these studies.

Though new generation antipsychotics have been associated with significantly lower propensity to cause EPSE, these agents are however linked with other serious problems such as dyslipidaemia and hyperglycaemia which imposes limitations to their use among a wide category of patients. Within the observation period of this study, there was no significant difference in the fasting lipid profile (FLP) and fasting blood sugar (FBS) level at baseline versus endpoint of study. This is in tandem with reports from pooled data which suggest that aripiprazole is neither associated with dyslipidaemia nor hyperglycaemia [22]. This favourable attribute indicates that aripiprazole is a potential treatment option for psychotic patients with co-morbid cardiovascular and or metabolic disorders.

Extra pyramidal side effects (EPSE) constitute a major shortcoming in the use of antipsychotics, especially the typical antipsychotics. Thus, it is desirable that an acceptable antipsychotic should have a favourable EPSE profile. In the current study, the EPSE profile from baseline to end point did not differ significantly. This is consistent with reports from other short term studies of aripiprazole [21,25,26]. This finding suggests a promising alternative therapeutic option for clinicians in the pharmacologic treatment of psychotic disorders in patients with known intolerance for EPSE inducing agents.

5. LIMITATIONS

Our findings should be viewed with the following limitations. First the proportion of patients who completed the study was small, the high drop-out rate was not envisaged, but comparison of socio-demographics was not different across those who dropped out or did not. Secondly, we did not assess for kidney and liver function (electrolytes urea and creatinine; liver function tests). Thirdly, we did not have a placebo group.

6. CONCLUSIONS

Overall, our data indicates that aripiprazole may be effective and well tolerated, with a favourable side effect profile among outpatients with first episode psychoses in Nigeria.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

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