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Therapeutic effectiveness and tolerability of aripiprazole as initial choice of treatment in first episode psychosis in an early intervention service: A one-year outcome study

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ABSTRACT

Introduction: Aripiprazole has been associated with a low prevalence of metabolic side effects as compared to other second generation antipsychotic (SGA) medications mostly in patients with long standing illness. The purpose of the present study was to assess specifically the effectiveness and safety of aripiprazole as a first choice for antipsychotic therapy for young patients presenting with a previously untreated first episode of a psychotic disorder (FEP).

Methods: Seventy-three patients presenting with a FEP and with minimal prior exposure to antipsychotic medications were recruited to be part of an open label naturalistic outcome study using aripiprazole as the first choice of antipsychotic medication. Data on positive, negative and total symptom severity including general psychopathological symptoms, level of functioning and metabolic indices were collected prospectively over a one-year period.

Results: As compared to baseline, patients treated with aripiprazole (mean dose 9.6 mg) improved significantly on measures of positive ($p < 0.001$), negative ($p < 0.001$) and total severity-general psychopathology symptoms ($p < 0.001$) and level of functioning ($p < 0.001$). Seventy two percent of the participants achieved positive symptom remission and 50% achieved total remission (positive and negative) at one year of follow up. Unlike reports on patients with longer standing illness, significant weight gain ($p < 0.001$) was observed, with 44% of participants experiencing >7% increase in body weight.

Conclusion: FEP patients starting treatment with aripiprazole improved on symptoms and social and occupational functioning. Aripiprazole was well tolerated except for a significant weight gain.

1. Introduction

While there is little variation in the effectiveness of second generation antipsychotic (SGA) medications for treatment of psychotic disorders, there is considerable variation in the nature and severity of metabolic side effects, with olanzapine and clozapine being associated with the largest increase in risk of metabolic syndrome (Young et al., 2015). When treating patients presenting with a first episode of a psychotic (FEP) disorder with little or no previous exposure to antipsychotic medications, clinicians are often guided by their existing knowledge about effectiveness and side effects of various antipsychotics available. The introduction of the newer SGAs such as aripiprazole (Harrison and Perry, 2004), lurasidone (Sanford, 2013) and ziprasidone (Harrison and Scott, 2006), with a possibly lower incidence of the metabolic syndrome, has widened the therapeutic choices.

The availability of metabolically safer but equally efficacious medications provides an opportunity to use a putatively "safer option" to initiate antipsychotic medication. It is in this broader, but practical, context that we conducted the present open label study for assessing the effectiveness and safety of initiating aripiprazole as a first choice SGA for patients with a psychotic disorder who present with little or no previous exposure to antipsychotic medications. Outcome over a period of one year was assessed on symptom dimensions, global and social functioning, and side effects.

2. Materials and methods

2.1. Setting

This study was carried out at an Early Intervention (EI) Program for Psychoses situated in south-west Montreal, Canada. It is the only such service for this defined catchment area (population 300,000) dedicated to assessment and treatment of all new cases of psychotic disorders (both affective and non-affective psychoses). As a publicly funded

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service, with no competing service in the catchment area, the sample of patients is close to a treated incidence sample (Iyer et al., 2015; Malla et al., 2003). The EI service accepts patients from any source, including self and family referrals for an initial assessment where a diagnosis of a FEP is made. Treatment is initiated either as an outpatient (47%) or following admission to the inpatient unit dedicated for FEP as part of the EI service.

2.2. Study participants

Although the program accepts patients 14–35 years old, participants for this study were 18 years or older with a diagnosis of a first episode of affective or non-affective (schizophrenia spectrum) psychotic disorder, as per the DSM-IV. Exclusion criteria were substance-induced psychosis, IQ < 70 or neurological disorders/head injuries; however, patients with concurrent substance abuse were included. Participants had received antipsychotic medication for no longer than one month at the time of entry to the treatment program assuring that all patients were still within their acute first episode. Participants were offered aripiprazole as the first choice at entry to the program. If the patient had received another antipsychotic prior to referral to PEPP-Montréal (usually in the emergency department), participants were offered a switch to aripiprazole upon entry to the treatment program as the first choice of treatment. Written informed consent was obtained from all participants soon after entry to the program. Research protocols and consent forms were approved by the Institutional Research Ethics Board.

As an open label naturalistic outcome study, clinicians were required to prescribe aripiprazole within a flexible dose range of 2–30 mg. Patients could be prescribed other psychiatric medications such as antidepressants, mood stabilizers or anti-anxiety medications if clinically deemed necessary.

2.3. Outcome measures

Data for this study were collected between 2010 and 2014. Assessments for each subject were performed over a 12 months period. Diagnosis was determined by Structured Clinical Interview for DSM-IV (SCID) (First, 2005) at entry and repeated at month 12. Duration of Untreated Psychosis (DUP) was determined using the Circumstances of Onset and Relapse Schedule (CORS) (Norman et al., 2004) a semi-structured interview that allows us to determine the onset, duration, and course of psychotic and other psychiatric symptoms, demographic and illness characteristics, and pathways to care. Symptoms were measured using Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993) at baseline (within 1 month of admission), months 1, 2, 3, 6, 9 & 12. All symptom assessments were carried out covering the preceding month. SAPS total score was calculated as the sum of the global scores of the four subscales: hallucinations, delusions, bizarre behavior and formal thought disorder. SANS total score was calculated as the sum of the global scores of the four subscales: affective flattening/blunting, alogia, apathy and asociality with the exclusion of the global rating of attention (Malla et al., 1993). BPRS total score is the sum of the totals of the four factors namely positive symptoms, negative symptoms, manic symptoms and depressive symptoms, which together represent total severity including general psychopathology. Functioning was measured using Global Assessment of Functioning Scale (GAF) (Bodlund et al., 1994) administered at the same time points as symptom assessments and Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992) conducted at baseline and month 12.

Remission and relapse were defined as follows: i. Positive Symptom Remission: no or mild positive psychotic symptoms (delusions, hallucinations, thought disorder and bizarre behavior) equivalent to a global rating of 2 or less on each of the global subscales on the SAPS, lasting for at least 1 month. ii. Total Remission: Both positive and negative symptoms are equivalent to a global rating of 2 or less on the global subscales of both SAPS and SANS for at least 1 month. iii. Relapse: recurrence of symptoms with the severity of at least 3 rated on one or more SAPS global items lasting at least 1 week plus need for change in treatment (Levy et al., 2012; Malla et al., 2008; Malla et al., 2006).

Neurological side effects were assessed using Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese, 2005) and Barnes Akathisia Scale (BAS) (Barnes, 1989) at the same time points as the symptom assessments. Body weight in kilograms was measured at baseline, months 1, 2, 3, 6, 9 & 12. Indices for metabolic measures, namely, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides were measured at baseline, months 3, 6 & 12. Fasting blood glucose level was measured at baseline and only at month 12, as changes in blood glucose levels are known to occur over much longer periods.

All prescriptions of antipsychotic, antidepressant, mood-stabilizer, and anti-anxiety medications were recorded. Adherence to medication was assessed monthly through reports from case managers and interviews with patients and/or families. Adherence was recorded on a 5-point scale; never = 0%, very infrequent = 25%, sometimes = 50%, quite often = 75% and always = 100%, indicating the proportion of time a patient was judged to be taking the antipsychotic medication as prescribed. Rate and time to discontinuation of aripiprazole was calculated. Aripiprazole was considered discontinued at the time it stopped being prescribed by the psychiatrist to the patient irrespective of the reasons for stopping.

2.4. Statistical analysis

Analyses were performed using SPSS, version 20 (SPSS Inc., Chicago, IL, USA). Means, standard deviations and frequencies were calculated for all study variables. Paired Sample *t*-test or Repeated Measures ANOVA with Bonferroni adjustment for multiple comparisons with time (7 levels) being the within-subjects factor was used to detect differences in outcome variables. Missing data were imputed using the Last Observation Carried Forward approach. All statistical tests were two sided, and a p value of 0.05 or less was considered significant.

3. Results

Seventy-three FEP patients were recruited for this study. Three participants withdrew from the study and one was withdrawn due to protocol violation; not taking aripiprazole. Data of a fifth participant were removed from the database because we had only baseline symptom assessment. The remaining 68 participants were included in the analysis (Fig. 1).

3.1. Description of the study sample

Demographic and clinical characteristics of our participating clients are shown in Table 1.

Two thirds of the participants had a diagnosis of a first episode of schizophrenia-spectrum psychoses and one-third was diagnosed with affective psychotic disorder with a median DUP of 13 weeks. Thirty eight percent of patients had concurrent substance abuse.

The mean dose for aripiprazole was 8.4 mg after initial dose titration was completed usually within one to two weeks. The mode for aripiprazole maintenance doses over one year of follow-up was determined for each patient. The mean and standard deviation of those modal doses were then calculated for the entire sample. Mean maintenance dose for aripiprazole was 9.6 mg (Table 1).

Average adherence to aripiprazole was 84%. Aripiprazole was discontinued for 34 (50%) patients at some time of the follow-up period. Of those, ten stopped the study before the end of one year: 2 at

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