Predictors of 'all cause discontinuation' of initial oral antipsychotic medication in first episode psychosis

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Abstract

Introduction: Discontinuation of the initial oral antipsychotic prescribed for a first episode of psychosis (FEP) can derail outcome. Our objective was to examine the rate of and time to all-cause discontinuation of the first antipsychotic prescribed and the factors influencing such discontinuation.

Methods: In a sample of 390 FEP patients, we estimated the rate of and time to discontinuation of the initial antipsychotic over a one-year period. The effects of a number of putative predictors of discontinuation were estimated using regression analyses.

Results: Rate of discontinuation of the first antipsychotic was 72%, with no difference between the 3 investigated antipsychotics (olanzapine (73%), risperidone (68%) and aripiprazole (75%)), (χ^2 (2) =1.89, p=.388). Mean time to discontinuation was 7.2 (4.6) months and was not different among the three antipsychotics (Log-rank χ^2 (2) = .257, p = .879). Binary logistic regression showed that higher positive and negative symptoms remission and baseline functioning were associated with lower rates of discontinuation (Nagelkerke R^2 = .36, χ^2 (10) = 66.9, p < .001). Multiple linear regression showed the same predictors, in addition to male gender and less weight gain per month of exposure to the initial antipsychotic, to be associated with longer time to discontinuation (adjusted R^2 = .336, F (9, 219) = 13.8, p < .001).

Conclusion: Discontinuation of the initial antipsychotic is a major concern in the course of treating FEP. Symptom relief, better functioning and lower side effects appear to be the major factors associated with continuing an antipsychotic medication.

Key words

Discontinuation, initial antipsychotic, remission, baseline functioning, weight gain

1.Introduction

Clinical Guidelines for treatment of a first episode of psychosis (FEP) promote the use of low-dose second-generation antipsychotics (SGAs) as the first-line pharmacological treatment. Despite proven efficacy and their judicious use in Early Intervention (EI) services, observations suggest a high rate of discontinuation of the initial antipsychotic medication used, with obvious consequences of increased risk of relapse, hospitalization and deterioration in functioning (Winton-Brown et al., 2017). Whale et al. (2016) reported a 73.3% all-cause discontinuation rate of initially prescribed antipsychotics during the first year of treatment of a FEP in a naturalistic clinical setting with no differences in rates reported between the commonly used SGAs, olanzapine (78.2%), quetiapine (69.2%), risperidone (66.3%) and aripiprazole (76.8) (Whale et al., 2016). Likewise, in the Comparison of Atypical antipsychotics in First Episode (CAFE) study, all-cause discontinuation rate of 70.3% was reported with no differences among olanzapine (68.4%), risperidone (71.4%) and quetiapine (70.9%) (McEvoy et al., 2007). Green et al (2006) also found a 76.6% all-cause discontinuation rate in FEP patients randomized to olanzapine (Green et al., 2006). These results from different samples of FEP are comparable to the 74% discontinuation rate reported by the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, the largest in chronic schizophrenia (Lieberman et al., 2005).

While medication discontinuation and lack of adherence to medication are recognized to be a problem throughout the course of illness in psychotic disorders, discontinuation of the first antipsychotic prescribed for treatment of a FEP may have special significance. For example, avoiding such interruption at the beginning of treatment may reduce the risk of relapse in the critical period of first two years following onset of a FEP (Birchwood et al., 1998) and allow other aspects of recovery such as, employment and return to pursuit of education to gain traction

and sustain momentum. Further, continuation of the first antipsychotic prescribed may also have cost implications as changing or temporary cessation of medications is likely be associated with both direct and indirect costs through increased risk of relapse and hospitalization.

Possible reasons for discontinuation of medication include lack of efficacy (Perkins et al., 2008) or conversely, extremely rapid resolution of symptoms (Kane et al., 2013; Steger et al., 2012) and inability to tolerate the side effects of the medication prescribed (Miller, 2008), such as weight gain. While efficacy of different SGAs as first line treatment in FEP appears to be relatively similar, weight gain is reported to be worse for olanzapine and less so for aripiprazole (Almandil et al., 2013); although in FEP patients aripiprazole has been reported to cause weight gain (Malla et al 2016). Apart from putative differential benefits (timely resolution of symptoms) or side effects of various antipsychotic medications, other factors that affect outcome may be equally important for determining risk of discontinuation of first antipsychotic prescribed. These less explored factors, known to influence outcome, include patient (e.g. sex, socio-economic status, level of functioning) or illness characteristics (e.g. DUP, premorbid adjustment) and environmental factors such as, cost. For example, it is possible that patients with better functioning at the time of entering treatment will understand the benefits of staying on one medication if it is working. If patients get relief from symptoms they are less likely to discontinue medication. On the other hand, young patients in treatment for the first time may exercise their agency by stopping their initial medication once they start feeling better or even without any apparent reason.

The outcome "all-cause discontinuation" of an antipsychotic medication is regarded as a global measure of overall antipsychotic effectiveness. This outcome metric is presumed to integrate both clinicians' and patients' perspectives on efficacy as well as safety of each medication. The

present study was conducted within a naturalistic outcome design embedded in an Early Intervention (EI) service for FEP, with the objective of examining the rate of, and the time to all-cause discontinuation of the first antipsychotic medication at the initiation of treatment and the factors that may influence such discontinuation. Such a design is known to improve the potential representativeness of randomized efficacy trials.

2. Materials and Methods

2.1. Setting

This study was conducted at the Prevention and Early Intervention Program for Psychoses (PEPP), at the Douglas Mental Health University Institute, Montreal, Canada. PEPP-Montreal is a publicly funded clinical academic program, which provides a specialized early intervention service to a defined catchment area in Southwest Montreal (population 300,000) while conducting extensive neurobiological, psychosocial and epidemiological research in FEP and early intervention. It is the only such service in the catchment area with no competing private or public facility. PEPP-Montreal assesses and treats all new cases of psychotic disorders (both affective and non-affective) within the catchment area, making the sample of patients close to a treated incidence sample. Patients are admitted to the EI program either directly as outpatients or through an initial admission to an inpatient unit of the hospital operated by the EI service (Pira et al., 2013). The hospitalized patients usually present initially at the hospital emergency department. All patients are followed regularly by a team comprising a psychiatrist and a case manager as outpatients and in the community for up to two years (Iyer et al., 2015).

2.2. Medication Protocol

This is a naturalistic outcome study with a flexible protocol for antipsychotic treatment prescribed by the treating clinician within a broader set of guidelines of using low dose SGA medications guided by availability (e.g. aripiprazole was not available until 2009), individual needs and tolerability, and patient preferences. Access to medication is assured through Québec's Pharmacare program or, in a smaller proportion, private (usually parental) medication insurance and minimizes variation in medication adherence attributable to patients' ability to pay. Other psychotropic medications such as antidepressants, mood stabilizers or anti-anxiety medications were prescribed, if clinically deemed necessary. Medication data were obtained monthly from carefully logged data in clinical records and transferred regularly to the main database for this study. If the patients had already started to respond to an antipsychotic prescribed prior to entry to PEPP, it was continued. However, if the patient had either not been taking any antipsychotics, taken an antipsychotic for a very brief period with no significant change or not been able to tolerate the medication taken prior to entry to the program, it was changed to a different SGA upon entry to the program.

While there is no clear guideline or restriction of prescribing olanzapine in FEP in Canada, there is an implicit understanding among clinicians, especially in the last few years, to avoid using olanzapine as first choice if alternatives are available. Our data covers a long period of 2003-2013 and at the beginning of the program only risperidone, quetiapine and olanzapine were available through the publicly funded system. With the introduction of aripiprazole in 2009 (and later other similar drugs), the program developed a general guideline to discuss with the patient the availability of drugs such as, aripiprazole, which may cause less weight gain or have less longer-term risk of developing a metabolic syndrome. This, so called, 'safety first' protocol was introduced as a guideline for physicians in the program around 2010.

Adherence to medication was assessed monthly through clinical reports from case managers and interviews conducted by research staff with patients and/or families. Adherence was recorded on a 5-point scale; never = 0%, very infrequent = 1-25%, sometimes = 26-50%, quite often = 51-75% and always = 76-100%, indicating the proportion of time a patient was judged to be taking the antipsychotic medication as prescribed. Patients were rated as adherent if they took their antipsychotic 75-100% of the time. This method has been shown to be reliable when compared to pill counting (Cassidy et al., 2010).

Given that the data reported here cover a period of 2003-2013, we tested for time trends in prescription patterns (see supplementary table 1). Risperidone and Olanzapine were prescribed with almost equal frequency between 2003 and 2009, and aripiprazole was prescribed in 64% of patients between 2010 and 2013, based on the perception and some published data that aripiprazole was associated with lower risk of metabolic syndrome and weight gain. The rate of prescription of risperidone and olanzapine dropped to 13% and 22%, respectively, between 2010 and 2013.

2.3. Participants

Participants were included if they were 14-35 years of age with an IQ greater than 70, had not received antipsychotic medication for more than 30 days, had been admitted to the program between January 2003 and Dec 2013 and had completed at least one year of treatment. Patients with substance-induced psychosis or neurological disorders/head injuries were not considered eligible for the treatment program. However, patients with co-morbid substance abuse were included. Demographic, clinical and medication data were collected prospectively throughout the follow-up period. These research procedures were thoroughly explained to all participants and written informed consent was obtained soon after entry to the program. In the case of patients

younger than 18 years, consent was signed by a parent or guardian in addition to assent by the patient. The research protocols were approved by the Douglas Mental Health University Institute Research Ethics Board for conducting all the assessments as part of the clinical research protocol at PEPP-Montréal.

Four hundred and eighty-six of the 571 patients (85%) consented to the PEPP research protocol. Patients were grouped based on their first antipsychotic medication prescribed upon entry to the program. Patients (n=390) whose treatment was initiated with oral olanzapine (n=169), risperidone (n=120) or aripiprazole (n=101) were the only ones included in the present analysis because the numbers of patients on other oral SGAs were too small to form distinct groups for comparison: quetiapine (n=29), paliperidone (n=8), ziprasidone (n=7), asenapine (n=3), loxapine (n=1), haloperidol (n=1) and perphenazine (n=1). Patients initiated on the long-acting injectable forms of risperidone (n=5), paliperidone (n=7) and zuclopenthixol (n=1) were also excluded from the analysis due to the invalidity of comparison with oral medications. The remaining cases (n=30) were either never prescribed or never agreed to take antipsychotic medication, or else their data were missing.

Participants admitted to the program as outpatients constituted 51% of the sample and 49% had their initial admission through an inpatient unit. Olanzapine was the initial antipsychotic for 38% of outpatients and 48% of inpatients, risperidone 34% and 28% and aripiprazole 28% and 24%, respectively.

2.4 Measures

Diagnosis was determined through administration of the Structured Clinical Interview for DSM-IV Axis I disorders (SCID) (First and Gibbon, 2004) at entry and repeated at month 12. Duration

of Untreated Psychosis (DUP), the time interval between the onset of the first threshold-level psychotic symptom and the start of adequate treatment with an antipsychotic for 1 month or until remission of psychotic symptoms, whichever comes first, was determined using the Circumstances of Onset and Relapse Schedule (CORS) (Norman et al., 2004). The latter is a semi-structured interview that helps determine the onset, duration, and course of psychotic and other psychiatric symptoms, demographic and illness characteristics, and pathways to care. Visible minority status was determined, using Statistics Canada criteria, as people who identify themselves as non-Aboriginal and non-Caucasian in race or non-white.

Symptoms were measured using Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) at baseline (within 1 month of admission) and months 1, 2, 3, 6, 9 and 12 after entry. Trained research assistants conducted symptom assessments after having achieved high levels of inter-rater reliability (range 0.75-0.92). Each assessment covered the preceding month. The SAPS total global score was calculated as the sum of the global scores of the four subscales: hallucinations, delusions, bizarre behavior and formal thought disorder. The SANS total global 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. Overall severity of symptoms was assessed with the Brief Psychiatric Rating Scale (BPRS) (Rhoades and Overall, 1988). Positive symptom remission was defined as having no or mild positive psychotic symptoms equivalent to a global rating of 2 or less on each of the global subscales on the SAPS (Andreasen et al., 2005), lasting for at least 1 month. Negative symptom remission was calculated in the same way using the SANS ratings. Remission data were collected monthly for the one-year period from baseline (intake) to month 12. For the purpose of this analysis, early remission (within the first 3 months)

and remission at the time of discontinuation were calculated. Functioning was measured using the Social and Occupational Functioning Scale (SOFAS) administered at baseline and month 12 (Goldman et al., 1992). Body weight in kilograms was measured at baseline and months 1, 2, 3, 6, 9 and 12. Due to the different length of exposure to medication for those who discontinued and those who did not, we calculated weight gain as proportionate to the months of exposure, expressed change in body weight per month of exposure to the initial antipsychotic.

2.5. Outcome variables

Rate of, and time to, discontinuation of the initial antipsychotic medication were the main outcome variables of this study. The index antipsychotic medication was considered discontinued at the time it stopped being prescribed by the psychiatrist or switched to another antipsychotic irrespective of the reasons for stopping or switching i.e. all-cause discontinuation. Rate (percentage) of discontinuation of the initially assigned antipsychotic during the one-year assessment period was calculated. Time to all-cause discontinuation was calculated as the duration in months from the date of the index prescription record until a prescription stop or switch to another antipsychotic. Patients were assessed by their psychiatrists once weekly for the first one month, every two weeks for the subsequent two months and, at least, once monthly thereafter. Patients were, however, followed by their respective case managers, much more frequently both within and without the clinic. Based on clinical needs and judgement of case managers the frequency of psychiatric assessments was adjusted.

2.6. Data Analysis

Analyses were performed using SPSS, version 23 (SPSS Inc., Chicago, IL, USA). Means, standard deviations and frequencies were calculated for all study variables. DUP values were

highly skewed and were normalized using log transformation. Pearson correlation was used to measure bivariate associations. Independent samples t-test, χ^2 test and one-way ANOVA were used for univariate analyses. Kaplan-Meier survival curves and log-rank test were used to assess time to all-cause medication discontinuation. Logistic regression was used to examine the influence of sex, visible minority status, log DUP, baseline functioning, type of antipsychotic, adherence, positive remission, negative remission and weight change on the rate of discontinuation. Linear regression was applied to test the same independent variables on time to discontinuation. Choice of the aforementioned predictors was based on our results from univariate analyses, in addition to previously established impact on outcomes (see above). Visible minority status was included as an independent variable because of reports of its association with rates of treatment attrition (Kreyenbuhl et al., 2009). All statistical tests were two-sided, and a p value of 0.05 or less was considered significant.

3. Results

3.1. Sample Description

Three hundred and ninety FEP patients were included in this study. Demographic and clinical characteristics of the study sample at baseline are shown in Table 1. Two-thirds of the participants had a diagnosis of a first-episode non-affective (schizophrenia-spectrum) psychotic disorder and one-third had a first-episode affective psychotic disorder. Half the patients had concurrent substance abuse.

Antipsychotic mean daily doses were 11.5 (6.5) mg for olanzapine, 2.2 (1.0) mg for risperidone and 10.8 (6.8) mg for aripiprazole. Three quarters (77%) of our sample took antipsychotic medication before PEPP entry for a mean duration of 18.3 (SD 15.3) days and a median of 15 days.

3.2. Medication discontinuation and potential predictors

3.2.1. Rate of discontinuation

Rate of discontinuation of the first oral antipsychotic prescribed in this sample was 72% (n=281). For 158 (56%) of discontinuation cases, the index antipsychotic was switched to another antipsychotic; whereas for 123 (44%), it was stopped for at least one month. The three antipsychotics tested were discontinued at similar rates; olanzapine (73%), risperidone (68%) and aripiprazole (75%), (χ^2 (2) =1.89, p=.388).

3.2.2. Time to discontinuation

Mean time to discontinuation was 7.2 (4.6) months. Kaplan-Meier survival curves for time to discontinuation by antipsychotic are shown in figure 1. Log-rank test did not reveal any significant difference (χ^2 (2) = .257, p = .879) in time to discontinuation across the three antipsychotics. Mean time to discontinuation was 7.5 (CI (95%): 6.8-8.2) months for olanzapine, 6.9 (range 6.1-7.9) months for risperidone and 7.2 (CI (95%): 6.3-8.0) months for aripiprazole. For the entire sample of patients treated in the EI service who had consented to research (n=486), discontinuation rate was 71% and mean time to discontinuation was 7.2 (4.6) months, similar to the sample that is included in this report (see methods).

3.3. Adherence and discontinuation

A majority (86%, n=334) of patients were adherent to their prescribed antipsychotics i.e. taking medication as prescribed 76-100% of the time. There was no significant difference in adherence between patients who discontinued (85%, n=238) or did not discontinue (88%, n=96) their first prescribed antipsychotic (χ^2 (1) =.61, p=.518). However, adherence was significantly lower in case of those who stopped (75%, n=91) compared to those who switched medication after discontinuation (93%, n=147) of the initial antipsychotic (χ^2 (1) =18.38, p=<.001).

3.4. Remission of symptoms and discontinuation

The rate of positive symptom remission was much lower in those who discontinued (40%, n=111/278) than those who did not (80%, n=84/105), (χ^2 (1) =48.97, p< .001). Rate of negative symptom remission was also lower in those who discontinued (19%, n=52/279) than those who did not (45%, n=49/108), (χ^2 (1) =28.85, p< .001). Early positive symptom remission (within the first 3 months) was lower in those who discontinued (62%, n=160/259) than those who did not discontinue (80%, n=87/109), (χ^2 (1) =11.31, p=.001). Early negative symptom remission was not different between those who discontinued (46%, n=95/207) and those who did not (50%, n=48/97), (χ^2 (1) =.34, p=.622).

3.5. Functioning and discontinuation

SOFAS score at baseline was 41.4 (12.8) on average corresponding to the category "serious impairment in social, occupational or school functioning". SOFAS at baseline was one category higher for those who did not discontinue [46.0 (12.9)] compared to those who discontinued [39.8 (12.4)], t (333) = 4.03, p < .001.

3.6. Weight gain and discontinuation

Average weight at baseline was 69.3 (14.4) kg. Body weight increased by a mean of 1.2 (1.8) kg per month of exposure to the initial antipsychotic. This was higher for those who discontinued [1.4 (2.2)] kg than those who did not discontinue [0.7 (0.6)], (t (245) = 4.19, p <.001). Weight change was not different between the three antipsychotics: olanzapine, risperidone and aripiprazole; F (2, 278) = 2.30, p = .103.

3.7. Visible minority status and discontinuation

Visible minority patients constituted 34.6% of our sample (n=135). The rate of discontinuation of the initial antipsychotic was 68.9 % (n=93/135) for visible minority and 73.5% (n=183/249) for non-visible minority patients (χ^2 (1) =.92, p=.344).

3.8. Multivariate analyses

3.8.1. Rate of discontinuation: Binary logistic regression with rate of discontinuation of the first prescribed antipsychotic as the dependent variable and sex, visible minority status, log DUP, baseline functioning, type of antipsychotic, adherence, positive remission, negative remission and weight change per month of exposure to the initial antipsychotic as the independent variables, was performed (Model 1a). The logistic regression model was significant, (χ^2 (10) = 66.9, p < .001). It explained 36% (Nagelkerke R^2) of the variance in discontinuation and correctly classified 79% of cases. The model revealed that higher positive remission, higher negative symptoms remission and higher baseline functioning were associated with lower rates of discontinuation. Adjusted odds ratios are shown in Table 2.

Positive remission at discontinuation and early positive remission are significantly correlated (r= .46, p < .001). Replacing positive and negative remission with early positive remission and early negative remission, respectively, resulted in a model (Model 1b) that was still significant (χ^2 (10) = 36.7, p < .001). It explained 24% (Nagelkerke R^2) of the variance in discontinuation and correctly classified 71% of cases. Male gender (p=.034), higher SOFAS at baseline (p < .001), higher early positive remission (p = .040) and less weight gain per month of antipsychotic (p=.049) were significantly associated with lower rates of discontinuation (supplementary table 2).

3.8.2. Time to discontinuation: Multiple linear regression was performed with time to discontinuation of the first prescribed antipsychotic as the dependent variable and sex, visible minority status, log DUP, SOFAS at baseline, type of antipsychotic, adherence and positive remission at discontinuation, negative remission at discontinuation and weight change per month of antipsychotic as the independent variables (Model 2a, Table 3). The model was significant ($F(9, 219) = 13.8$, $p < .001$, adjusted $R^2 = .336$) with male gender, higher baseline functioning, higher positive remission, higher negative remission and less weight gain per month of antipsychotic showing significant association with longer time to discontinuation.

Replacing positive and negative remission at discontinuation with early positive remission and early negative remission, respectively, resulted in a model (Model 2b) that was still significant ($F(9, 183) = 5.7$, $p <.001$, adjusted $R^2 = .182$). Predictors for longer time to discontinuation were male gender ($p=.006$), higher SOFAS at baseline ($p = .020$) and less weight gain per month of antipsychotic ($p < .001$) (supplementary table 3).

3.9. Stopped versus switched sub-group analysis

Sub-group analyses revealed significant differences at the time of entry to the treatment program and at discontinuation between patients who stopped the antipsychotic and those who switched from their initial antipsychotic medication to a different one (Table 4). These differences suggest that the former group had a more favourable profile on symptoms and functioning compared to the latter. Repeating the logistic regression model 1a with patients who *stopped* the initial antipsychotic showed that higher negative symptoms remission at discontinuation and higher functioning at baseline were associated with lower rates of discontinuation (supplementary table 4). With patients who *switched* the initial antipsychotic, logistic regression showed that higher positive remission at discontinuation and higher functioning at baseline were associated with less

discontinuation rate. Patients experiencing positive remission were 9 times less likely to discontinue their initial antipsychotic medication (supplementary table 5).

Linear regression model 2a with patients who *stopped* showed higher positive remission at discontinuation and less weight gain per month of antipsychotic to predict longer times to discontinuation (supplementary table 6) whereas repeating the model with those who *switched* showed male gender, higher baseline functioning, positive remission and less weight gain to be significant predictors of longer time to discontinuation (supplementary table 7).

4. Discussion

In a large sample of FEP patients, with minimal prior exposure to antipsychotic medication, we have observed a relatively high rate (72%) of "all-cause" discontinuation of the first antipsychotic prescribed at the time of initiating treatment in an EI service. We did not observe any difference in the rate of or time to discontinuation between three commonly used SGAs; olanzapine, risperidone and aripiprazole. Our results are in agreement with previous findings (Green et al., 2006; Whale et al., 2016).

Higher baseline functioning, positive symptom remission, negative symptom remission, less weight gain and male gender seemed to be the protective factors against discontinuation affecting both the rate of as well as time to discontinuation. It is noteworthy that remission of positive and to slightly lesser extent negative symptoms showed a high level of association with the outcome of discontinuation suggesting that if patients experience sustained relief of symptoms they are less likely to discontinue medication. Therefore, antipsychotic medications are likely to be discontinued because of lack of relief from symptoms and not because of complete and early relief of symptoms. Remission of negative symptoms was observed to be a

relatively weaker predictor of time to medication discontinuation, which is likely related to relatively less impact of antipsychotic medications on negative symptoms.

Baseline functioning is closely related to outcomes in psychosis. It may partly reflect pre-morbid functioning and generally portends better response to treatment, higher level of adherence to medication and lower relapse rates as well as better functional outcome (Alvarez-Jimenez et al., 2012; Carrion et al., 2013; Diaz-Caneja et al., 2015; Malla et al., 2002; Spellmann et al., 2012). Indeed, in this study, higher level of functioning at baseline was associated with a lower discontinuation rate and longer time to discontinuation with the first antipsychotic prescribed. Given that higher baseline social and occupational functioning was an independent predictor of rate and time to discontinuation of first antipsychotic medication prescribed, it is unlikely to be explained entirely by higher adherence to medication or higher rate of remission. The practical implication could be that patients with a low functioning status at the time of first treatment may require greater effort from the service providers to keep them engaged in treatment and to closely monitor their response to medication.

The propensity to gain weight is associated with all SGAs, including aripiprazole, for patients with limited prior exposure to antipsychotic medications (Malla et al., 2016; Miller, 2008). We observed that weight gain was associated particularly with time to discontinuation, with those gaining weight likely to discontinue medication early in the course of their treatment.

Although belonging to an ethnic minority group has been linked to treatment disengagement (Kreyenbuhl et al., 2009), the all-cause discontinuation rate in this study was not different for patients who identified themselves as visible minority. This might imply an equal level of satisfaction on the part of patients with the care received, including pharmacotherapy, regardless of their ethnic background.

Medication discontinuation led to stopping or switching to another medication almost in equal proportions. It is likely that patients who stop medication may be influenced by different factors than those who switch to a different antipsychotic medication. In our exploration of this question through a sub-group post-hoc analysis, we observed that although the two subgroups differed on several measures, generally favouring those who stopped, the factors associated with discontinuation were rather similar for both. Remission of positive symptoms seems to be an important factor in determining either the rate or time to discontinuation. Those who switched may be more influenced by concerns about lack of relief of negative symptoms and poor functioning, the two variables likely most related to each other.

5. Strengths and limitations

The strengths of our study include a very large sample of FEP patients from a real-world setting, who were in the acute phase of their first episode with very limited prior exposure to antipsychotic medications and represented most, possibly not all, treated cases of FEP from a defined catchment area population. The sample has been very well characterized with frequent structured assessments carried out prospectively by trained independent raters not involved in patients' care. Limitations of this naturalistic study are that the assignment to each antipsychotic medication was not random nor was there a strict protocol for administrating the dose and type of medication. However, the objective of our investigation was to examine effectiveness of the first medication prescribed when patients enter treatment within a typical EI service for FEP. Another limitation is that we did not record reasons for treatment discontinuation. Prescriptions could be missing from clinical records for reasons other than treatment discontinuation such as missing an appointment. Unlike previous reports (Miller, 2008), adherence did not contribute to rate of or time to discontinuation in this study when entered in regression models. This may be partly the

result of a ceiling effect of high rates of adherence achieved in an EI service characterized by a low patient-to-case manager (20:1) as has been reported in the past in relation to effect of medication adherence on remission in another EI service (Malla et al., 2006). It is also possible that adherence was over-reported in the present study although our method of measuring adherence was shown to be reliable in previous studies (Cassidy et al., 2010). The best possible method would be to measure blood antipsychotic level, albeit, invasive to patients and therefore impractical for a routine clinical service.

6. Conclusion

Findings of the present study confirm that discontinuation of the initial antipsychotic medication prescribed, irrespective of the cause, is a major concern in the course of treating FEP. The high discontinuation rate observed in our study suggests that treatments, currently available or our approach to treatment, may not adequately address the needs and preferences of most individuals with FEP. Relief of symptoms appears to be the major incentive for continuing an antipsychotic medication. Hence, achieving remission, especially of positive symptoms, early in the course of treatment is a desirable goal and may require careful monitoring and additional interventions such as, cognitive behavioural therapy, especially for patients with poor baseline functioning and lack of adequate response to medication. Patients with poor baseline functioning may require additional psychosocial interventions to keep them engaged in treatment.

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Tables

Table 1. Patient characteristics at baseline

Variable	Mean (SD) or n (valid %)
Demographic characteristics	
Age at entry	23.4 (4.5)
Male	279 (72%)
Single	352 (91%)
Post-secondary education (completed high school)	188 (50%)
Visible minority	135 (35%)
Illness characteristics	
Schizophrenia-spectrum primary diagnosis	274 (71%)
Substance abuse secondary diagnosis	208 (56%)
DUP (weeks)	Mean 53.7 (105.2) Median = 16.1
SAPS (Global)	11.6 (3.2)
SANS (Global)	10.2 (3.8)
BPRS (Total)	67.1 (13.0)
SOFAS	41.4 (12.8)

DUP = Duration of untreated psychosis
SAPS = Scale for the Assessment of Positive Symptoms; total global scores range from 0 to 20 with higher scores indicating more severe symptoms
SANS = Scale for the Assessment of Negative Symptoms; total global scores range from 0 to 20 after removal of the items for attention with higher scores indicating more severe symptoms
BPRS = Brief Psychiatric Rating Scale; total scores range from 24 to 168, with higher scores indicating more severe symptoms
SOFAS = Social and Occupational Functioning Assessment Scale; total scores range from 0 to 100, with higher scores indicating greater functioning

Table 2. Logistic regression with rate of discontinuation of the first prescribed antipsychotic as the outcome (Model 1a)

	Rate of discontinuation			
	Odds ratio	**95% CI**	**χ^2**	**p**
Sex[a]	.49	.23-1.06	3.30	.069
Visible minority status[b]	1.11	.53-2.32	.08	.778
Log DUP	.81	.45-1.45	.51	.475
SOFAS at baseline	.95	.93-.98	12.01	.001
Group/antipsychotic[c]			.82	.663
Olanzapine	1.23	.50-3.06	.20	.654
Risperidone	.85	.33-2.18	.11	.736
Adherence[d]	1.14	.39-3.33	.06	.805
Positive remission at discontinuation[e]	5.14	2.40-11.01	17.75	.001
Negative remission at discontinuation[f]	3.00	1.40-6.41	7.99	.005
Weight change per month	1.27	.93-1.75	2.26	1.33

[a]Reference: Female, [b]Reference: Visible minority, [c]Reference: Aripiprazole, [d]Reference: Adherent, [e]Reference: In positive remission at discontinuation, [f]Reference: In negative remission at discontinuation

The odds of discontinuation is 5 times lower with positive remission and 3 times lower with negative remission at discontinuation and decreases by 5% for every unit increase in SOFAS score at baseline.

Table 3. Linear regression with time to discontinuation of the first prescribed antipsychotic as the outcome (Model 2a)

	Time to Discontinuation				
	B	**SE**	**Standardized Beta**	**T**	**p**
Sex	-1.41	.56	-.14	-2.51	.013
Visible minority	-.44	.54	-.05	-.81	.419
Log DUP	.37	.42	.05	.86	.389
SOFAS at baseline	.05	.02	.13	2.30	.022
Group/antipsychotic	-.35	.34	-.06	-1.02	.311
Adherence	.02	.84	.001	.02	.982
Positive remission at discontinuation	3.62	.53	.40	6.78	<.001
Negative remission at discontinuation	1.67	.64	.15	2.59	.010
Weight change at discontinuation	-.61	.14	-.25	-4.37	<.001

Male gender, higher baseline functioning, higher positive remission and negative remission at discontinuation and less weight gain per month of antipsychotic are significantly associated with longer time to discontinuation.

Table 4: Differences between patients who stopped or switched their initial antipsychotic

Variable (Mean (SD) or n (%))	Stopped (n=123)	Switched (n=158)	p
Age at entry	24.1 (4.7)	22.8 (4.3)	.010
SANS (Global)	9.3 (4.0)	11.0 (3.6)	<.001
SOFAS	42.7 (13.1)	37.6 (11.3)	.001
Early negative remission	51 (60%)	44 (36%)	.001
Positive remission at discontinuation	61 (51%)	50 (32%)	.001
Negative remission at discontinuation	30 (25%)	22 (14%)	.029
Antipsychotic prior to PEPP entry	78 (68%)	128 (83%)	.005
Adherence			
Admitted to PEPP from inpatient unit	53 (43%)	92 (59%)	.016
Time to discontinuation (month)	5.5 (3.3)	4.7 (3.5)	.050

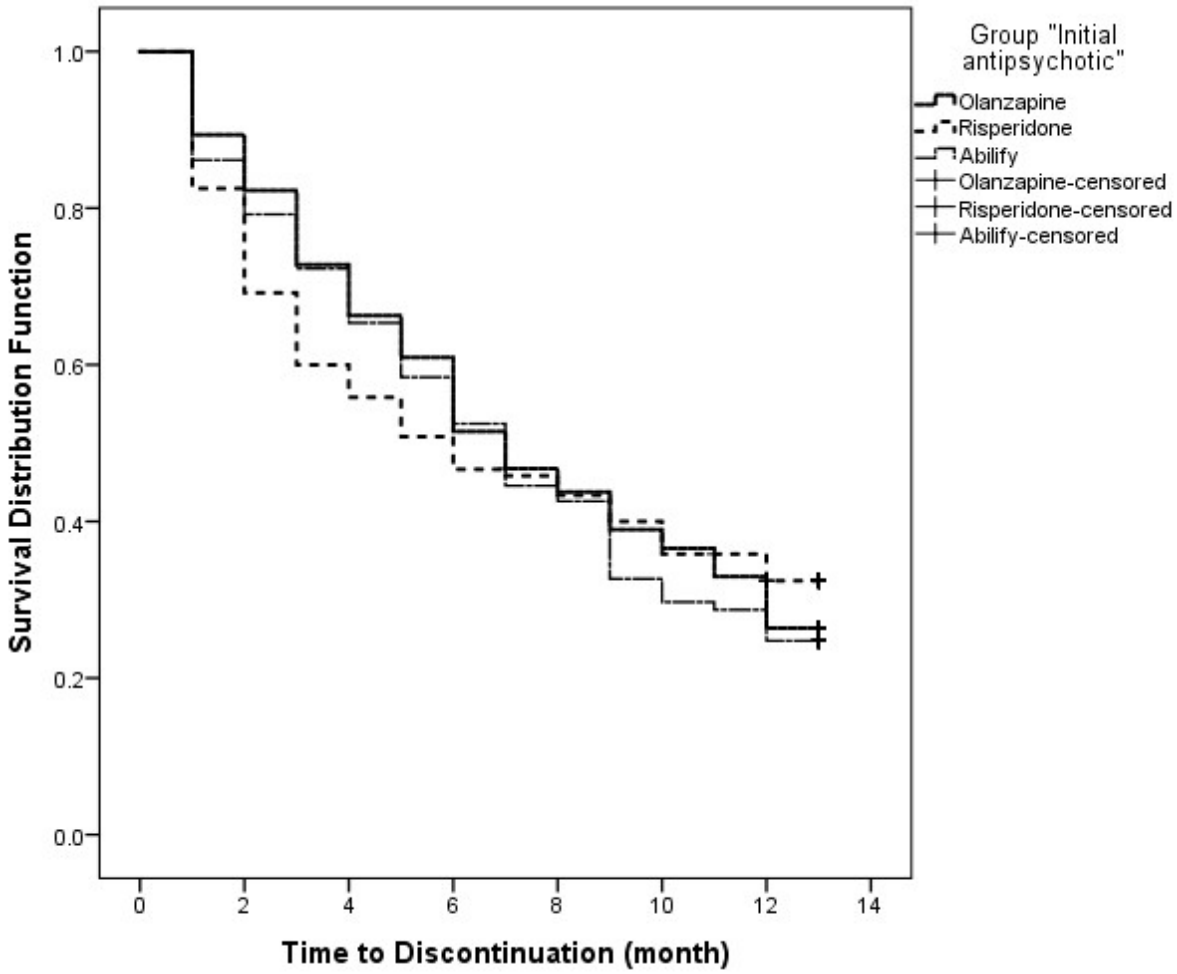

Figure 1: Kaplan-Meier estimated survival curves by antipsychotic

Supplementary Tables

Supplementary table 1: Time trends in antipsychotic prescription

			Group "Initial antipsychotic"		
			Olanzapine	Risperidone	Aripiprazole
Year	2003-2006	Count	82	56	0
		%	59.4%	40.6%	0.0%
	2007-2009	Count	52	43	1
		%	54.2%	44.8%	1.0%
	2010-2013	Count	35	21	100
		%	22.4%	13.5%	64.1%

Supplementary table 2. Logistic regression with rate of discontinuation of the first prescribed antipsychotic as the outcome (Model 1b)

	Rate of discontinuation			
	Odds ratio	**95% CI**	**χ^2**	**p**
Sex[a]	.43	.20-.94	4.52	.034
Visible minority status[b]	1.32	.62-2.81	.53	.466
Log DUP	.67	.36-1.24	1.64	.200
SOFAS at baseline	.95	.93-.98	12.44	<.001
Group/antipsychotic[c]			3.96	.138
Olanzapine	2.49	1.01-6.09	3.96	.047
Risperidone	1.75	.69-4.43	1.40	.236
Adherence[d]	2.16	.74-6.30	2.00	.157
Early positive remission[e]	2.34	1.04-5.28	4.20	.040
Early negative remission[f]	1.28	.62-2.63	.43	.511
Weight change per month of antipsychotic	1.35	1.00-1.81	3.86	.049

[a]Reference: Female, [b]Reference: Visible minority, [c]Reference: Aripiprazole, [d]Reference: Adherent, [e]Reference: In early positive remission, [f]Reference: In early negative remission

Supplementary table 3. Linear regression with time to discontinuation of the first prescribed antipsychotic as the outcome (Model 2b)

	Time to Discontinuation				
	B	**SE**	**Standardized Beta**	**T**	**p**
Sex	-1.92	.69	-.19	-2.77	.006
Visible minority	-.28	.68	-.03	-.41	.681
Log DUP	.66	.55	.09	1.20	.233
SOFAS at baseline	.06	.02	.16	2.36	.020
Group/antipsychotic	.16	.42	.03	.39	.694
Adherence	1.28	.97	.09	1.33	.187
Early positive remission	1.19	.70	.12	1.70	.091
Early negative remission	1.25	.67	.13	1.88	.062
Weight change per month of antipsychotic	-.81	.16	-.34	-4.95	<.001

Supplementary table 4. Logistic regression with rate of discontinuation of the first prescribed antipsychotic as the outcome for patients who stopped the initial antipsychotic

	Rate of discontinuation			
	Odds ratio	**95% CI**	**χ^2**	**p**
Sex[a]	.45	.18-1.13	2.86	.091
Visible minority status[b]	1.17	.46-2.93	.11	.746
Log DUP	.78	.40-1.54	.51	.473
SOFAS at baseline	.96	.93-1.00	4.67	.031
Group/antipsychotic[c]			3.63	.163
Olanzapine	1.01	.34-3.02	.00	.983
Risperidone	.40	.12-1.30	2.35	.126
Adherence[d]	2.10	.63-7.01	1.44	.230
Positive remission at discontinuation[e]	2.13	.81-5.64	2.33	.127
Negative remission at discontinuation[f]	3.33	1.30-8.53	6.26	.012
Weight change per month	1.45	.83-2.53	1.74	.187

[a]Reference: Female, [b]Reference: Visible minority, [c]Reference: Aripiprazole, [d]Reference: Adherent, [e]Reference: In positive remission at discontinuation, [f]Reference: In negative remission at discontinuation

The odds of discontinuation is 3 times lower with negative remission at discontinuation and decreases by 4% for every unit increase in SOFAS score at baseline.

Regression Model 1c: $\chi^2 = 26.11$, df=10, sig. = .004, Nagelkerke $R^2 = .25$

Supplementary table 5. Logistic regression with rate of discontinuation of the first prescribed antipsychotic as the outcome for patients who switched the initial antipsychotic

	Rate of discontinuation			
	Odds ratio	**95% CI**	**χ^2**	**p**
Sex[a]	.42	.16-1.08	3.25	.071
Visible minority status[b]	.95	.40-2.28	.01	.909
Log DUP	.84	.41-1.69	.25	.619
SOFAS at baseline	.93	.90-.97	13.78	<.001
Group/antipsychotic[c]			1.14	.566
Olanzapine	1.55	.51-4.72	.59	.442
Risperidone	1.86	.59-5.81	1.13	.287
Adherence[d]	.93	.21-4.07	.01	.919
Positive remission at discontinuation[e]	9.29	3.88-22.27	24.99	<.001
Negative remission at discontinuation[f]	2.39	.92-6.19	3.21	.073
Weight change per month	1.28	.92-1.80	2.13	.144

[a]Reference: Female, [b]Reference: Visible minority, [c]Reference: Aripiprazole, [d]Reference: Adherent, [e]Reference: In positive remission at discontinuation, [f]Reference: In negative remission at discontinuation

The odds of discontinuation is 9 times lower with positive remission at discontinuation and decreases by 7% for every unit increase in SOFAS score at baseline.

Regression Model 1c: $\chi^2 = 81.88$, df=10, sig. <.001, Nagelkerke $R^2 = .51$

Supplementary table 6. Linear regression with time to discontinuation of the first prescribed antipsychotic as the outcome for patients who stopped the initial antipsychotic

	Time to Discontinuation				
	B	**SE**	**Standardized Beta**	**T**	**p**
Sex	-1.25	.74	-.15	-1.70	.092
Visible minority	-.14	.72	-.02	-.20	.843
Log DUP	.19	.55	.03	.34	.732
SOFAS at baseline	.04	.03	.14	1.54	.126
Group/antipsychotic	-.17	.44	-.04	-.40	.693
Adherence	.87	1.02	.08	.85	.397
Positive remission at discontinuation	2.16	.81	.25	2.66	.009
Negative remission at discontinuation	1.31	.73	.16	1.81	.073
Weight change at discontinuation	-.98	.46	-.19	-2.16	.033

Regression Model 2c: F (9, 117) = 2.9, p =.004, adjusted R^2 = .118

Supplementary table 7. Linear regression with time to discontinuation of the first prescribed antipsychotic as the outcome for patients who switched the initial antipsychotic

	Time to Discontinuation				
	B	**SE**	**Standardized Beta**	**T**	**p**
Sex	-1.51	.65	-.14	-2.31	.022
Visible minority	-.55	.62	-.05	-.90	.371
Log DUP	.29	.48	.04	.60	.548
SOFAS at baseline	.06	.02	.16	2.56	.011
Group/antipsychotic	-.20	.39	-.03	-.53	.598
Adherence	-.18	1.08	-.01	-.17	.868
Positive remission at discontinuation	4.38	.63	.45	7.01	<.001
Negative remission at discontinuation	1.38	.74	.12	1.86	.064
Weight change at discontinuation	-.61	.15	-.26	-4.22	<.001

Regression Model 2c: $F(9, 164) = 14.95$, $p < .001$, adjusted $R^2 = .420$