Psychiatry Research 273 (2019) 631–640

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

# Rates and predictors of one-year antipsychotic treatment discontinuation in first-episode schizophrenia: Results from an open-label, randomized, "real world" clinical trial

Cheng Zhang[a,1], Yuan Yanbo[a,1], Han Xue[a], Yang Lei[a], Zeng Xin[b], Yang Fude[c], Lu Zheng[d], Wang Chuanyue[e], Deng Hong[f], Zhao Jingping[g], Xiang Yu-Tao[h], Christoph U. Correll[i,j,k], Yu Xin[a,*]

[a] Institute of Mental Health, Peking University, Huayuanbei 51, Haidian District, Beijing, 100191, China
[b] Peking University Clinical Research Institute, Beijing, China
[c] Beijing Hui-Long-Guan Hospital, Beijing, China
[d] Tongji Hospital of Tongji University, Shanghai, China
[e] Beijing Anding Hospital, Capital Medical University, Beijing, China
[f] West China Hospital, Sichuan University, Chengdu, China
[g] Mental Health Institute, Second Xiangya Hospital, Central South University, Changsha, China
[h] Unit of Psychiatry, Faculty of Health Science, University of Macau, Macao SAR, China
[i] The Zucker Hillside Hospital, Psychiatry Research, Northwell Health, Glen Oaks, NY, USA
[j] Hofstra Northwell School of Medicine, Hempstead, NY, USA
[k] The Feinstein Institute for Medical Research, Manhasset, NY, USA

ARTICLE INFO

*Keywords:*
First-episode
Schizophrenia
Antipsychotic
Discontinuation
Predictors

ABSTRACT

Antipsychotic treatment discontinuation is a major challenge in the treatment of first-episode schizophrenia (FES) patients. However, the rate and predictors remain unclear. Five hundred and sixty-nine FES patients were randomized to risperidone ($n$ = 190), olanzapine ($n$ = 185) or aripiprazole ($n$ = 194) in a six-site study in China with 1-year follow-up. Patients failing the initially assigned antipsychotic were switched to one of the other 2 antipsychotics. By 52 weeks, 47.1% of FES patients discontinued all antipsychotics. In the 8-week acute phase, an antipsychotic switch was protective against antipsychotic discontinuation, whereas higher positive symptoms at the endpoint predicted discontinuation. In the maintenance phase, discontinuation was predicted by male gender and higher CGI-S score at the endpoint. The findings indicate that in China nearly half of patients with FES discontinued antipsychotic treatment during one year treatment. Clinicians should employ strategies other than medication choice to keep them from discontinuing.

## 1. Introduction

Two decades ago, Robinson and colleagues found out that patients with FES had high rates of response to antipsychotic treatment (Robinson et al., 1999a). The responsiveness had been confirmed in a recent systemic review and meta-analysis (Zhu et al., 2017). However, treatment discontinuation in FES patients benefiting from antipsychotic treatment was found to increase relapse rates nearly 5-fold (Robinson et al., 1999b). A recent study from Finnish population-based registers suggested that the risk of treatment failure or relapse after discontinuation of antipsychotic use does not decrease during the first 8 years of illness (Tiihonen et al., 2018). Antipsychotic treatment discontinuation is a major challenge in the treatment of FES (Emsley et al., 2013).

Several studies focusing on discontinuation of a specific antipsychotic in FES patients (Crespo-Facorro et al., 2012, 2014; Kahn et al., 2008; Mustafa et al., 2018; San et al., 2012) have found certain advantages of second generation antipsychotics (SGAs) over first generation antipsychotics (FGAs), but no substantial differences in efficacy were found among SGAs. However, individuals with schizophrenia may

* Corresponding author.
*E-mail addresses:* chengzhang_8899@163.com (Z. Cheng), yuanyb@gmail.com (Y. Yuan), shirleyhan599@gmail.com (X. Han), 13718747842@163.com (L. Yang), 13651329721@163.com (X. Zeng), yangfd200@126.com (F. Yang), luzheng@mail.tongji.edu.cn (Z. Lu), wang.cy@163.net (C. Wang), rhdeng88@hotmail.com (H. Deng), zhaojingpingcsu@163.com (J. Zhao), xyutly@gmail.com (Y.-T. Xiang), ccorrell@lij.edu (C.U. Correll), yuxin@bjmu.edu.cn (X. Yu).
[1] These authors contributed equally.

https://doi.org/10.1016/j.psychres.2019.01.068
Received 2 May 2018; Received in revised form 16 January 2019; Accepted 23 January 2019
Available online 24 January 2019

go through several different antipsychotics before finding a medication with the appropriate efficacy and tolerability. About one-third of FES patients require a change in medication within their first year of treatment (Perez-Iglesias et al., 2008). To date, patients undergoing a medication switch have seldom been included in antipsychotic efficacy studies. Reports analyzing antipsychotic treatment discontinuation are also limited.

A recent retrospective study from the UK reported that more than half of patients with first-episode psychosis discontinue their antipsychotic treatment within a 1.5-year follow-up period (Winton-Brown et al., 2017). The aim of this study was to prospectively examine the rates and associated predictors of antipsychotic treatment discontinuation in FES patients. We hypothesized that approximately half of the patients with FES would discontinue antipsychotic treatment within the first year. In addition, we speculated that the factors contributing to antipsychotic treatment discontinuation would be demographic or clinical characteristics rather than medication choice. Because there were different needs to be addressed at different stages with symptom alleviation in the acute phase and relapse prevention and rehabilitation in the maintenance phase, we would examine discontinuation predictors in the acute and the maintenance phases, respectively.

## 2. Methods

### 2.1. Participants and setting

The details of the study design has been described elsewhere (Han et al., 2014). Briefly, this was a 1-year randomized, open-labeled clinical trial conducted in 6 major psychiatric hospitals in China. Three hospitals were in the North, and the other three were in the South. Although all of the six Centers were in urban regions, they provide service to both patients from urban and rural areas. This was a secondary analysis of a RCT database. The primary outcome in the original RCT was the baseline-to-endpoint change in PANSS total score. The main paper was in submission process.

Patients meeting the following inclusion criteria were recruited: (1) aged between 18 and 45 years; (2) inpatients or outpatients; (3) diagnosis of schizophrenia by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) Axis I Disorder, patient edition (SCID-I/P); (4) illness duration $\leq 3$ years (The onset was determined in the SCID-I/P according to when the first symptom appeared); 5) continuous antipsychotic treatment $< 4$ weeks and cumulative length of antipsychotic treatment $< 12$ weeks, with no prior exposure to long-acting antipsychotic injection; 6) the ability to understand the contents of the interview and provide written informed consent. Exclusion criteria included: 1) current major medical conditions; 2) current or lifetime history of alcohol/drug abuse or dependence; 3) contraindication to olanzapine, aripiprazole or risperidone. After complete description of the study to the subjects, written informed consent was obtained. The trial was approved by the ethics committees of the participating centers.

### 2.2. Treatment

To mimic the reality of clinical practice, we employed a 3-phase design. Phase 1 was a randomization phase (comparison of the three drugs will be published in another paper from the same research team). Eligible patients were randomly assigned to a risperidone (3–6 mg/day), olanzapine (10–25 mg/day) or aripiprazole (15–30 mg/day) group, with a stratified block randomization based on a pre-established scheme and stratified by study center. The randomization table and program were generated with SAS (version 9.2) by a clinical epidemiologist who was not involved in the trial design. The doses of risperidone, olanzapine and aripiprazole were chosen based on the Treatment Guideline for Schizophrenia in China (Shu, 2007). Patients who showed little or no benefit from the Phase 1 treatment were allowed to enter Phase 2. Patients undergoing a medication switch entered Phase 2, which was allowed as early as week 4 in the case of non-responders, defined as a PANSS reduction $< 50\%$, symptom exacerbation, severe impulsiveness, agitation, suicide risk, or intolerability (including clinically relevant weight gain) (Han et al., 2014). The change in antipsychotic regimen was restricted to the three SGAs in the study (risperidone, olanzapine and aripiprazole); drug choices were made by research psychiatrists based on their clinical experience (e.g. patients who were overweight should avoid olanzapine). Patients who did not respond to the second SGA were allowed to enter Phase 3, which allowed the research psychiatrists to introduce other antipsychotics such as clozapine and augmentation or antipsychotic polypharmacy. Following the Treatment Guidelines for Schizophrenia in China (Shu, 2007), the acute phase was defined as the first 8 weeks of treatment, and the following period was considered as the maintenance phase.

Oral benzhexol (2–6 mg/day) or promethazine (25–75 mg/day) could be prescribed, but not preventively. Adjunctive lorazepam (0.5–1.5 mg/day) was also permitted if necessary. This design was aimed to keep the patients on antipsychotic treatment for as long as possible and to maximize the possibility of completing the follow up.

All the participants received basic psychosocial support like in the daily psychiatric service.

### 2.3. Assessment and evaluation

Basic demographic and clinical characteristics were collected with a standard data collection form designed specifically for this study. Psychopathology was measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987)and Clinical Global Impressions-Severity Scale (CGI-S) (Spearing et al., 1997). Side effects were measured by the Udvalg for KliniskeUndersogelser Side Effect Rating Scale (UKU) (Lingiaerde et al., 1987). Drug attitude was assessed by the Drug Attitude Inventory (DAI) (Hogan et al., 1983). Function was evaluated by the Personal and Social Performance Scale (PSP) (Tianmei et al., 2011). Recruited patients were evaluated by a trained psychiatrist in each hospital at the baseline and weeks 4, 8, 12, 26, 39 and 52.

There were 2-3 psychiatrists responsible for clinical assessment at each site. All interviewers attended a 1-week training workshop on use of the rating instruments (including PANSS, CGI-S, UKU, DAI and PSP etc.) prior to the study and reached a high level of consistency (intraclass correlation coefficients or kappa values $> 0.75$). They were not necessarily blind to the original randomization of the treatments.

### 2.4. Primary and secondary outcomes

The primary outcome was the all-cause antipsychotic treatment discontinuation rate within 52 weeks, which was defined as (1) discontinuation of antipsychotics regardless of follow-up completion, or (2) early discontinuation of the follow-up (patients who missed follow-ups and then returned were considered as continuation, as long as they remained on the antipsychotic during the missed period). Secondary outcomes included all-cause antipsychotic treatment discontinuation at week 8, the discontinuation rate of the Phase 1 antipsychotics, medication switch rate and the predictors of all-cause antipsychotic treatment discontinuation during both the acute ($\leq 8$ weeks) and the maintenance (8–52 weeks) phase.

### 2.5. Statistical methods

Kaplan-Meier curves were used to estimate the time to antipsychotic treatment discontinuation during the 52-week follow-up. Cox proportional hazards regression analysis was used to estimate associations of

demographic and clinical variables with antipsychotic treatment discontinuation in the acute and maintenance phases.

Demographic variables, the PANSS, PSP, UKU and DAI ratings at baseline and 8-week (ratings at endpoint were used if discontinuation occurred before 8-week) were included for the acute phase univariate analysis. Demographic variables and the PANSS, PSP, UKU and DAI ratings at 8- week (the baseline for the maintenance phase) and at 52-week (ratings at endpoint were used if discontinuation occurred before 52-week) were included for the maintenance phase univariate analysis. The changes of the PANSS total score at the 4- and 8-week follow-up assessments (Schennach et al., 2013; Leucht and Zhao, 2014) were also included for the acute and the maintenance phase analyses, respectively. Variables which turned out to be significant in univariate analysis were included in multivariate analysis. A stepwise approach was used and the probability for stepwise was set at 0.05. Last-observation-carried-Forward analysis was used to manage the missing data for variables which were repeatedly measured during follow-up. The significance level was set at 0.05 (two tailed). All analyses were conducted in the intent-to-treat sample (Cox proportional hazards regression analysis in the maintenance phase was conducted in patients who went through the 8-week follow-up).

## 3. Results

### 3.1. Patient characteristics and disposition

A total of 580 patients were screened and 569 met the study criteria and participated in this study (Fig. 1). There were no significant differences among the three groups with regard to both basic demographic and clinical characteristics including PANSS and functioning except for the UKU neurological and other subscales at baseline, although there were differences of borderline significance in the CGI-S (Table 1).

### 3.2. Rates of antipsychotic treatment discontinuation

A total of 268 patients (47.1%) discontinued antipsychotic treatment at the end of the 52-week follow-up (Table 2). There were no significant differences among the three initial treatment groups in terms of all-cause antipsychotic treatment discontinuation (risperidone 54.9% vs. olanzapine 47.1% vs. aripiprazole 56.1%, $\chi^2 = 2.47$, df = 2, $p = 0.291$) (Fig. 2). And 124 (21.8%) patients discontinued antipsychotic treatment during the 8-week acute phase. Totally, 363 patients (63.8%) discontinued their originally assigned antipsychotics, 139 patients of which underwent antipsychotic switch during the 52-week follow-up. Most switches (59.0%) occurred during the 8-week acute phase (Table 2). The antipsychotic treatment discontinuation rate was much greater in patients with originally assigned antipsychotics than in patients after drug switch (52.1% (224/430) vs. 31.7% (44/

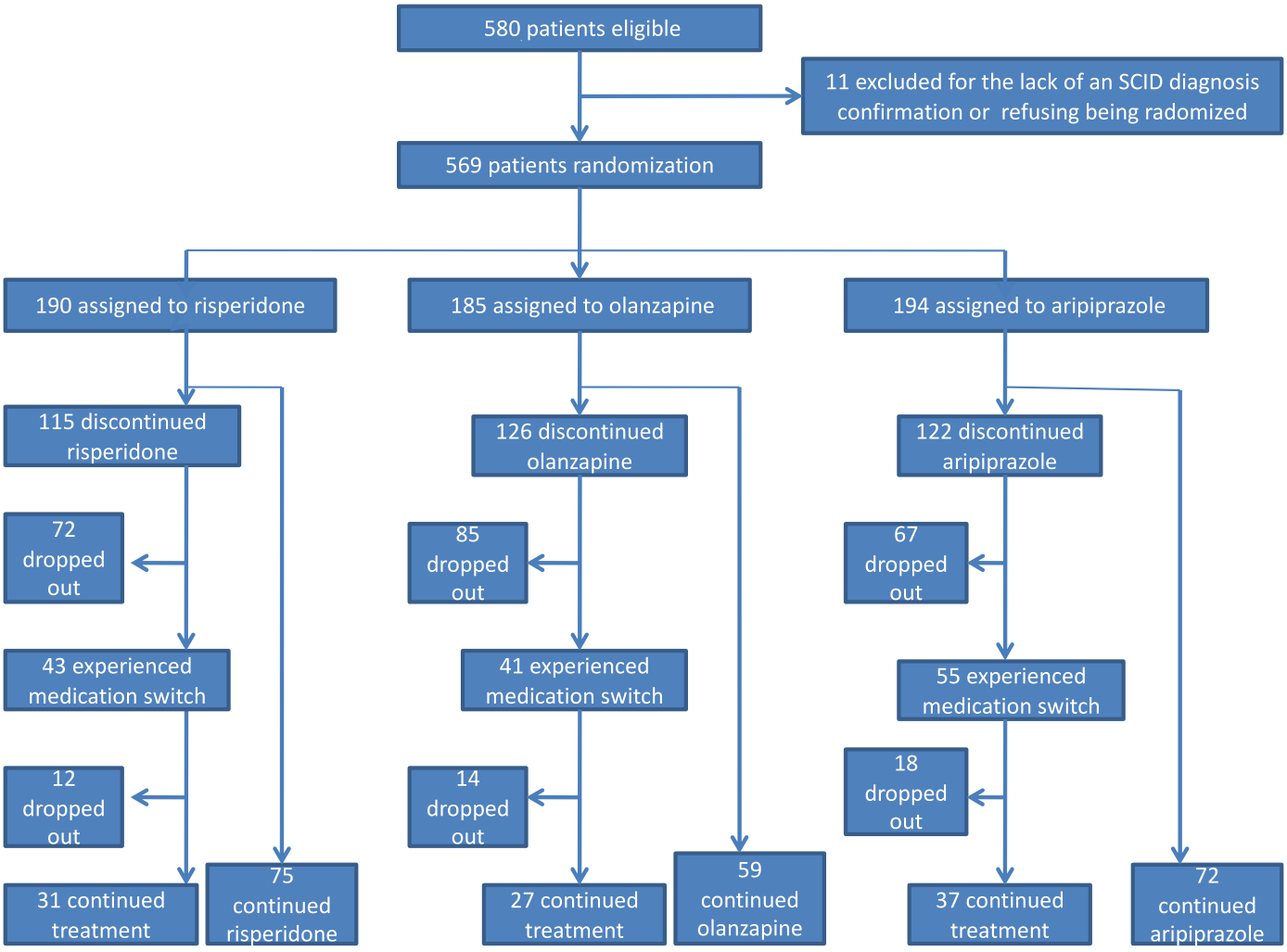


**Fig. 1.** Patient disposition.

**Table 1**
Baseline characteristics of the patients.

| | Risperidone (*N* = 190) | Olanzapine (*N* = 185) | Aripiprazole (*N* = 194) | Total (*N* = 569) | *P* |
|---|---|---|---|---|---|
| Sociodemographic characteristics | | | | | |
| Age (years) | 25.2 (7.1) | 24.8 (7.6) | 25.1 (7.1) | 25.0 (7.3) | 0.573 |
| Women | 90/190 (47%) | 96/185 (52%) | 100/194 (52%) | 286/569 (50%) | 0.619 |
| Education | | | | | |
| Elementary school | 6/187 (3%) | 7/181 (4%) | 7/193 (4%) | 20/561 (4%) | 0.544 |
| Middle school | 43/187 (23%) | 45/181 (25%) | 36/193 (19%) | 124/561 (22%) | |
| High school | 45/187 (24%) | 45/181 (25%) | 60/193 (31%) | 150/561 (27%) | |
| Technical secondary school | 21 /187 (11%) | 25/181 (14%) | 19/193 (10%) | 65/561 (12%) | |
| College | 30/187 (16%) | 24/181 (13%) | 25/193 (13%) | 79/561 (14%) | |
| Bachelor and above | 42/187 (22%) | 35/181 (19%) | 46/193 (24%) | 123/561 (22%) | |
| Illness duration (months) | 12.3 (10.3) | 10.8 (11.7) | 11.5 (12.2) | 11.5 (11.4) | 0.102 |
| Family history of psychiatric disorders | 31/190 (16%) | 29/185 (16%) | 32/194 (16%) | 92/569 (16%) | 0.975 |
| Baseline characteristics | | | | | |
| CGI | 5.36 (0.07) | 5.45 (0.73) | 5.30 (0.71) | 5.37 (0.72) | 0.056 |
| Mild | 2/187 (1%) | 2/184 (1%) | 0/193 (0%) | 4/564 (1%) | |
| Moderate | 13/187 (7%) | 15/184 (8%) | 22/193 (11%) | 50/564 (9%) | |
| Obvious | 91/187 (49%) | 70/184 (38%) | 92/193 (48%) | 253/564 (45%) | |
| Severe | 73/187 (39%) | 91/184 (49%) | 68/193 (35%) | 232/564 (41%) | |
| Extremely severe | 5/187 (3%) | 5/184 (3%) | 5/193 (3%) | 15/564 (3%) | |
| Psychopathology score (PANSS) | | | | | |
| Total | 87.1 (14.5) | 86.0 (14.6) | 85.8 (15.4) | 86.3 (14.9) | 0.642 |
| Positive subscale | 23.7 (5.6) | 23.4 (5.2) | 23.2 (5.4) | 23.4 (5.4) | 0.562 |
| Negative subscale | 21.6 (7.4) | 21.0 (7.9) | 20.6 (7.0) | 21.1 (7.4) | 0.486 |
| General psychopathology subscale | 41.7 (7.6) | 41.7 (7.5) | 42.0 (8.6) | 41.8 (7.9) | 0.980 |
| Insight item | 5.4 (1.1) | 5.4 (1.0) | 5.3 (1.0) | 5.4 (1.0) | 0.510 |
| PSP | 41.4 (13.2) | 40.4 (13.3) | 42.8 (12.8) | 41.6 (13.1) | 0.229 |
| UKU | | | | | |
| Psychological | 2.2 (2.7) | 2.5 (2.7) | 2.1 (3.0) | 2.3 (2.8) | 0.060 |
| Neurological | 0.9 (1.3) | 0.5 (0.8) | 1.0 (1.5) | 0.8 (1.3) | 0.003 |
| Autonomic | 0.9 (1.7) | 1.0 (1.5) | 0.9 (2.0) | 0.9 (1.8) | 0.280 |
| Other | 0.8 (1.2) | 0.9 (1.1) | 0.6 (1.6) | 0.8 (1.3) | < 0.0-01 |

*Note:* PANSS = positive and negative syndrome scale. Theoretical scores range from 30 to 210 (total score), from 7 to 49 (positive scale), from 7 to 49 (negative scale), and from 16 to 112 (general psychopathology scale). Higher scores indicate more severe psychopathology. CGI = clinical global impression. Higher scores indicate more severe psychopathology. UKU = udvalg for kliniskeundersogelser. PSP = personal and social performance scale. Higher scores indicate better function. The UKU has four subscales: 1) psychic side effects (concentration difficulties, asthenia/lassitude, sleepiness/sedation, failing memory, depression, anxiety, increased duration of sleep, reduced duration of sleep, increased dream activity, apathy); 2) neurological side effects (dystonia, rigidity, hypokinesia/akinesia, hyperkinesia, tremor, akathisia, epileptic seizures, paraesthesias); 3) autonomic side effects (disturbance of accommodation, increased salivation, reduced salivation, nausea/vomiting, diarrhea, constipation, disturbance of micturition, polyuria/polydipsia, orthostatic dizziness, palpitations/tachycardia, increased sweating), and 4) other side effects (rash, pruritus, photosensitivity, increased pigmentation, reduced pigmentation, weight gain, weight loss, menorrhoea, amenorrhoea, galactorrhoea, gynecomastia, increased sexual desire, reduced sexual desire, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, dryness of vagina, headache, physical dependence, psychic dependence). DAI = Drug attitude was assessed by the Drug Attitude Inventory.

139), $p < 0.01$).

### 3.3. Predictors of acute-phase antipsychotic treatment discontinuation

There were 124 patients of antipsychotic treatment discontinuation in the acute phase. Antipsychotic switch, PSP, PANSS total score reduction and UKU-other score at the endpoint were negatively associated with antipsychotic treatment discontinuation, while scores of CGI-S, PANSS positive, negative, general psychopathological sub-scales and insight item at endpoint were positively associated with antipsychotic treatment discontinuation. However, only antipsychotic switch, PANSS positive score at the endpoint remained significant in multivariate analysis (Table 3).

### 3.4. Predictors of maintenance-phase antipsychotic treatment discontinuation

Male gender, CGI-S, PANSS positive, negative and general psychopathological scale and insight item score at endpoint were positively associated with antipsychotic treatment discontinuation. In addition, PSP, PANSS total score reduction at the endpoint and DAI score at both 8-week and endpoint were negatively associated with antipsychotic treatment discontinuation. However, only male gender and CGI-S score remained significant in multivariate analysis (Table 4).

## 4. Discussion

To our knowledge, this is the first prospective study that investigated antipsychotic treatment discontinuation and its contributing factors in a large sample of FES patients with minimal prior antipsychotic exposure. We found that nearly half of the patients discontinued antipsychotic treatment during the first year. In addition, medication choice, including the initial randomly assigned antipsychotic and the antipsychotic in use immediately prior to discontinuation, had no significant impact on antipsychotic treatment discontinuation during the first year of treatment. In the acute phase, patients with more positive symptoms were more likely to discontinue antipsychotic treatment, whereas a switch to another antipsychotic decreased the risk of discontinuation by nearly 80%. During the maintenance phase, male patients were more likely to discontinue antipsychotic treatment than female patients, and more overall symptoms increased the risk of discontinuing antipsychotic treatment.

To date, very few studies focusing on antipsychotic discontinuation have allowed sequential antipsychotic trials, which represents the real situation in clinical care for FES patients experiencing medication inefficacy or intolerance, though studies on discontinuation of a specific antipsychotic are abundant. One study comprising 55 discharged FES Chinese patients showed a discontinuation rate of 55% (Tang and Liu, 2009). A recent retrospective study of FES patients reported that

**Table 2**
Treatment discontinuation at different time points.

| Treatment Outcome | 4 weeks ($n=569$) | 8 weeks ($n=569$) | 12 weeks ($n=569$) | 26 weeks ($n=569$) | 39 weeks ($n=569$) | 52 weeks ($n=569$) |
|---|---|---|---|---|---|---|
| **Discontinuation of any antipsychotic treatment, *n* (%)** | **89 (15.6%)** | **124 (21.8%)** | **173 (30.4%)** | **220 (38.7%)** | **261 (45.9%)** | **268 (47.1%)** |
| Discontinuation of initially assigned antipsychotic, *n* (%) | 86 (15.1%) | 116 (20.4%) | 158 (27.8%) | 191 (33.6%) | 220 (38.7%) | 224 (39.4%) |
| Discontinuation after antipsychotic medication switch *n* (%) | 3 (0.5%) | 8 (1.4%) | 15 (2.6%) | 29 (5.1%) | 41 (7.2%) | 44 (7.7%) |
| **Continuation of any antipsychotic treatment, *n* (%)** | **480 (84.4%)** | **445 (78.2%)** | **396 (69.6%)** | **349 (61.4%)** | **308 (54.2%)** | **301 (52.9%)** |
| Continuation of initially assigned antipsychotic, *n* (%) | 433 (76.1%) | 371 (65.2%) | 308 (54.1%) | 257 (45.2%) | 212 (37.3%) | 206 (36.2%) |
| Continuation after antipsychotic medication switch, *n* (%) | 47 (8.3%) | 74 (13.0%) | 88 (15.5%) | 92 (16.2%) | 96 (16.9%) | 95 (16.7%) |

58% halt treatment within a 1.5-year follow-up period (Winton-Brown et al., 2017). Data from the EUFEST showed that only 15.7% discontinued antipsychotic treatment, however patients lost to follow-up, which reached 31.3%, might also be discontinuers (Landolt et al., 2016). In the present prospective study, we observed a 47.1% discontinuation rate, which seemed comparable with rates in western population in the two studies mentioned above, however, more studies were needed to clarify whether there was difference between different populations. It confirmed a high risk of antipsychotic treatment discontinuation in the first year. This high rate indicates that a considerable proportion of patients who responded to antipsychotics stopped taking their medication. Previous studies have primarily focused on differences among individual medications in all-cause discontinuation, whereas antipsychotic treatment discontinuation was neglected.

### *4.1. Influence of antipsychotic choices on antipsychotic treatment discontinuation*

As we hypothesized, neither the initial medication nor the medication being used immediately prior to discontinuation was predictive of discontinuation. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial found an advantage of olanzapine over risperidone and quetiapine in the time to all-cause discontinuation in chronic schizophrenia patients (Lieberman et al., 2005) (although this was only true in patients re-randomized to olanzapine but not in those switched to other antipsychotics (Essock et al., 2006)). No significant difference was found among different SGAs in time to treatment discontinuation in most FES studies (Crespo-Facorro et al., 2012; Kahn et al., 2008; San et al., 2012), which matches the findings in the current study. These data indicate that specific treatment strategies are needed beyond the choice of antipsychotics to ensure patients maintain their medications.

### *4.2. Influence of demographic characteristics on antipsychotic discontinuation*

Demographic characteristics did not predict antipsychotic discontinuation in the acute phase, however, the risk of antipsychotic treatment discontinuation in male patients was more than one and a half-fold as great as in female patients in the maintenance phase. Although most patients were younger, which might lead to a floor effect of age, age, gender and education did not predict antipsychotic discontinuation in most studies focusing on original study medications (Gaebel et al., 2010; McEvoy et al., 2007). However, a 10-year prospective study found that male gender was a risk factor associated with antipsychotic treatment discontinuation (Jung et al., 2011). It suggested that male gender predicted antipsychotic treatment discontinuation rather than discontinuation of the original antipsychotics. However, gender was not a predictor of antipsychotic treatment discontinuation in the EUFEST study (Landolt et al., 2016). It might due to the differences between Asian and European population, which needs further studies to clarify. Thus, male patients might require more medication monitoring and should have more frequent appointments with psychiatrists, especially after the acute phase and in Asian population.

### *4.3. Influence of clinical characteristics on antipsychotic treatment discontinuation*

Clinical characteristics at baseline, including illness duration and family history of psychiatric disorders, symptoms, and social function did not predict antipsychotic discontinuation in both the acute and the maintenance phase. Severe positive symptoms, negative symptoms, general psychopathological symptoms and overall symptoms and poor insight at the endpoint were positively associated with antipsychotic treatment discontinuation in both the acute and the maintenance phase.

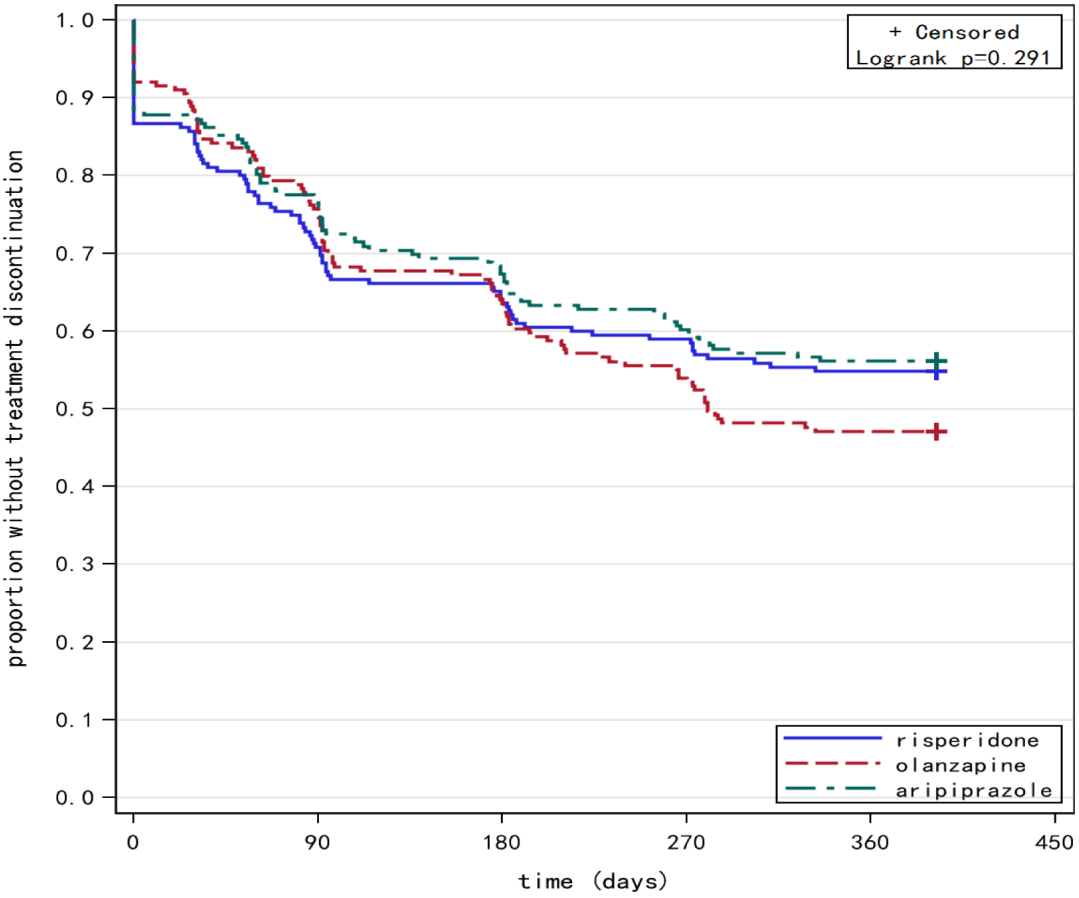


**Fig. 2.** Time to treatment discontinuation because of any cause.

Good social function and more symptom reduction at the endpoint were negatively associated with antipsychotic treatment discontinuation in both the acute and the maintenance phase. Positive drug attitude was negatively associated with antipsychotic treatment discontinuation in the maintenance phase rather than the acute phase. However, most of them seemed mediated by other factors, except positive symptoms in the acute phase and overall symptoms in the maintenance phase.

One study on acute schizophrenia patients found that positive symptoms were the most important factor influencing antipsychotic discontinuation, followed by adverse events (Ascher-Syanum et al., 2010). Our data suggested that severe positive symptoms with PANSS increased the risk of antipsychotic treatment discontinuation in the acute phase. Thus, in the acute phase, one possible strategy for maintaining patients on the medication is to attenuate the positive symptoms as soon as possible. Medication switch, which was shown to be a protective factor against discontinuation in the acute phase, may be a useful option for patients who do not sufficiently respond to the initial antipsychotic within a few weeks. Faries and colleagues also revealed that a higher percentage of patients completed a 1-year follow-up after switching away from their first antipsychotics compared with patients who maintained their initial drugs (Faries et al., 2008). Although medication switch is usually considered after 4–6 weeks of treatment at a therapeutic dosage, many treatment guidelines have recommended an optimal switch time point from 2 to 6 weeks (Buchanan et al., 2010; Leucht et al., 2011). Some studies even found antipsychotic non-responders could switch medication as early as within the first 2 weeks (Derks et al., 2010; Leucht and Zhao, 2014). Convincing evidence showed that little or no improvement in the first 2 weeks of antipsychotic treatment is a reliable predictor of non-response at the 6- to 12-week assessment point (Correll et al., 2011; Samara et al., 2015). Although FES data are less robust compared with chronic schizophrenia (Samara et al., 2015), lack of treatment response after the first 2 weeks of a therapeutic dosage has been suggested to prompt an antipsychotic switch. This more positive attitude towards medication switch is supported by the findings in the present study.

Side effects did not predict antipsychotic treatment discontinuation in our data, except that UKU-other subscale score at the endpoint was negatively correlated with antipsychotic treatment discontinuation in univariate analysis in the acute phase. Several RCTs reported that side effect was one of the most important reasons why patients discontinued study medications (Khan et al., 2008). One prospective study demonstrated that less weight gain was associated with longer time to discontinuation of the original antipsychotics in FES patients (Mustafa et al., 2018). It seemed that although side effects increased the risk of discontinuation of original study medications, it might not increase the risk of discontinuation of all antipsychotic medication. In other words, most of FES patients discontinuing study medications due to side effects might try another antipsychotic rather than discontinuing antipsychotic treatment.

We found that poor insight could increase the likelihood of antipsychotic treatment discontinuation, while positive drug attitude (evaluated by DAI) could decrease it. However, the significance of both in univariate analysis disappeared in multivariate analysis. Poor insight has been considered a risk factor of medication non-adherence in psychotic patients (Kane et al., 2013). Data from the EUFEST study showed that DAI score may be a predictor for discontinuation of the initiated treatment (Gaebel et al., 2010). Our results showed a similar effect of DAI score in this multiple treatment trial in the maintenance phase rather than in the acute phase. However, the significance of insight and drug attitude was likely to be mediated by overall symptoms immediately prior to discontinuation.

This is the first prospective study to investigate antipsychotic

**Table 3**
Predictors in the acute phase of treatment for all antipsychotic treatment discontinuation.

| | Univariate analysis | | | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|---|---|
| | HR | 95%CI | | *P* | HR | 95%CI | | *P* |
| Age | 0.991 | 0.953 | 1.030 | 0.6423 | | | | |
| Gender (male) | 0.778 | 0.437 | 1.382 | 0.3910 | | | | |
| Education | | | | | | | | |
| Middle school | 0.681 | 0.149 | 3.107 | 0.6197 | | | | |
| High school | 0.833 | 0.189 | 3.665 | 0.8088 | | | | |
| Technical secondary school | 0.910 | 0.189 | 4.381 | 0.9065 | | | | |
| College | 0.435 | 0.080 | 2.377 | 0.3371 | | | | |
| Bachelor and above | 0.690 | 0.151 | 3.150 | 0.6322 | | | | |
| Family history of psychiatric disorders | 0.667 | 0.283 | 1.571 | 0.3544 | | | | |
| Illness duration | 0.994 | 0.968 | 1.020 | 0.6475 | | | | |
| **Baseline characteristics** | | | | | | | | |
| Group | | | | | | | | |
| Risperidone | | | | | | | | |
| Olanzapine | 0.961 | 0.470 | 1.965 | 0.9126 | | | | |
| Aripiprazole | 1.077 | 0.538 | 2.157 | 0.8342 | | | | |
| CGI-S | 0.775 | 0.514 | 1.169 | 0.2250 | | | | |
| PANSS-p | 1.013 | 0.958 | 1.071 | 0.6475 | | | | |
| PANSS-n | 0.980 | 0.942 | 1.020 | 0.3170 | | | | |
| PANSS-g | 0.974 | 0.938 | 1.011 | 0.1630 | | | | |
| Insight | 0.906 | 0.691 | 1.188 | 0.4739 | | | | |
| PSP | 0.994 | 0.972 | 1.016 | 0.5826 | | | | |
| DAI | 1.055 | 0.939 | 1.185 | 0.3665 | | | | |
| UKU-psychic | 0.868 | 0.751 | 1.003 | 0.0557 | | | | |
| UKU-neurological | 0.923 | 0.710 | 1.200 | 0.5487 | | | | |
| UKU-autonomic | 0.897 | 0.728 | 1.104 | 0.3036 | | | | |
| UKU-other | 0.714 | 0.502 | 1.016 | 0.0616 | | | | |
| **Rating prior to discontinuation or at week 8** | | | | | | | | |
| Medication switch | 0.416 | 0.186 | 0.928 | 0.0321 | 0.211 | 0.086 | 0.517 | 0.0007 |
| Medication | | | | | | | | |
| Risperidone | | | | | | | | |
| Olanzapine | 1.190 | 0.592 | 2.392 | 0.6253 | | | | |
| Aripiprazole | 1.298 | 0.610 | 2.761 | 0.4987 | | | | |
| Other antipsychotic | 0.000 | 0.000 | | 0.9902 | | | | |
| Combination therapy | 0.000 | 0.000 | | 0.9887 | | | | |
| Early response | 0.650 | 0.361 | 1.170 | 0.1509 | | | | |
| CGI-S | 1.513 | 1.176 | 1.947 | 0.0013 | | | | |
| PANSS-p | 1.084 | 1.037 | 1.132 | 0.0003 | 1.134 | 1.079 | 1.191 | < 0.0001 |
| PANSS-n | 1.050 | 1.002 | 1.101 | 0.0430 | | | | |
| PANSS-g | 1.066 | 1.026 | 1.106 | 0.0010 | | | | |
| Insight | 1.339 | 1.083 | 1.655 | 0.0070 | | | | |
| PSP | 0.963 | 0.944 | 0.983 | 0.0003 | | | | |
| PANSS total score reduction | 0.970 | 0.955 | 0.984 | < 0.0001 | | | | |
| DAI | 0.882 | 0.778 | 1.001 | 0.0514 | | | | |
| UKU-psychic | 0.924 | 0.808 | 1.056 | 0.2454 | | | | |
| UKU-neurological | 1.097 | 0.860 | 1.399 | 0.4552 | | | | |
| UKU-autonomic | 0.942 | 0.756 | 1.172 | 0.5894 | | | | |
| UKU-other | 0.662 | 0.472 | 0.929 | 0.0172 | | | | |

*Note:* HR = Hazard Ratio. Other abbreviations are explained in the first footnote to Table 1.

treatment discontinuation and its predictors in a large sample of FES patients. A three-phase design (with a multi-centre, randomized, controlled trial as its first phase) was employed to mimic the "real world" of daily practice. However, the results of this study should be interpreted with cautions due to several methodological limitations. First, open-label nature might lead to biases in clinical assessments, although no specific antipsychotic was found to be better than another in our data. Second, FES patients should be maintained on antipsychotics for at least 1 to 2 years (Leucht et al., 2011). The present study lasted for only one year, therefore, rates of the long-term treatment discontinuation in FES patients was not analyzed in this study. Third, we used a different definition of discontinuation than traditional RCT studies evaluating discontinuation of an assigned medication. This could make our results less comparable to traditional RCT studies. However, this definition served our purpose of exploring factors contributing to antipsychotic treatment discontinuation in FES patients and may also complement findings from traditional RCT studies. Fourth, patients who did not continue the follow-up evaluations were considered to have discontinued antipsychotics. It is possible that some patients may have received treatment from other psychiatric hospitals. Nonetheless, when selecting the six participating centers, we included the largest and most reputable local psychiatric medical centers. Additionally, a rather flexible study design was employed to maximize the possibility of maintaining patients on their treatment. Fifth, the 1-year all-cause antipsychotic treatment discontinuation rate is relatively high, at nearly 50%. However, this is comparable with the results from another perspective study with a small sample of discharged Chinese FES patients (Tang and Liu, 2009) and another recent retrospective study from England (Winton-Brown et al., 2017). We did not obtain detailed data on whether antipsychotics were discontinued due to intolerability or inefficacy. Post-hoc analysis suggested that 1 in 3 patients discontinued antipsychotics following ≥50% total symptom reduction and symptom remission, indicating that a considerable proportion of patients who were satisfied with the treatment outcome discontinued their antipsychotic treatment. In China, a substantial number of remitted schizophrenia patients discontinued their treatment because of a lack of education on medication management for patients and their caregivers (Huang and Wang, 2011). Other developing countries may

**Table 4**
Predictors of all antipsychotic treatment discontinuation in the maintenance treatment phase.

| | Multivariate analysis HR | Multivariate analysis 95%CI | Multivariate analysis | Multivariate analysis *P* | Multivariate analysis HR | 95%CI | | *P* |
|---|---|---|---|---|---|---|---|---|
| Age | 1.004 | 0.979 | 1.030 | 0.7500 | | | | |
| Gender (male) | 1.844 | 1.224 | 2.777 | 0.0034 | 1.607 | 1.065 | 2.424 | 0.0237 |
| Education | | | | | | | | |
| Middle school | 1.017 | 0.306 | 3.378 | 0.9779 | | | | |
| High school | 0.645 | 0.191 | 2.169 | 0.4781 | | | | |
| Technical secondary school | 0.810 | 0.229 | 2.872 | 0.7445 | | | | |
| College | 0.340 | 0.088 | 1.314 | 0.1176 | | | | |
| Bachelor and above | 0.878 | 0.267 | 2.888 | 0.8304 | | | | |
| Family history of psychiatric disorders | 0.866 | 0.524 | 1.433 | 0.5764 | | | | |
| Illness duration | 1.001 | 0.986 | 1.017 | 0.8579 | | | | |
| **Rating at 8-week** | | | | | | | | |
| CGI-S | 1.052 | 0.880 | 1.259 | 0.5783 | | | | |
| PANSS-p | 0.997 | 0.955 | 1.040 | 0.8786 | | | | |
| PANSS-n 1.010 | | 0.977 | 1.044 | 0.5486 | | | | |
| PANSS-g | 0.996 | 0.965 | 1.027 | 0.7903 | | | | |
| Insight | 0.997 | 0.865 | 1.150 | 0.9709 | | | | |
| PANSS improvement | 0.999 | 0.990 | 1.008 | 0.8250 | | | | |
| PSP | 0.997 | 0.981 | 1.013 | 0.7107 | | | | |
| DAI | 0.879 | 0.807 | 0.958 | 0.0033 | | | | |
| UKU-psychic | 1.026 | 0.955 | 1.102 | 0.4897 | | | | |
| UKU-neurological | 1.128 | 0.946 | 1.345 | 0.1813 | | | | |
| UKU-autonomic | 1.047 | 0.916 | 1.196 | 0.5030 | | | | |
| UKU-other | 1.108 | 0.979 | 1.253 | 0.1043 | | | | |
| Medication | | | | | | | | |
| Risperidone | | | | | | | | |
| Olanzapine | 1.017 | 0.633 | 1.633 | 0.9447 | | | | |
| Aripiprazole | 0.716 | 0.410 | 1.250 | 0.2396 | | | | |
| Other antipsychotic | 0.000 | 0.000 | 0.000 | 0.9853 | | | | |
| Combination therapy | 2.051 | 0.625 | 6.726 | 0.2360 | | | | |
| **Rating at the end** | | | | | | | | |
| Medication switch | 0.758 | 0.474 | 1.214 | 0.2493 | | | | |
| CGI-S | 1.654 | 1.419 | 1.927 | < 0.0001 | 1.628 | 1.394 | 1.902 | < 0.00-01 |
| PANSS-p | 1.104 | 1.067 | 1.143 | < 0.0001 | | | | |
| PANSS-n 1.045 | | 1.008 | 1.083 | 0.0155 | | | | |
| PANSS-g | 1.082 | 1.051 | 1.113 | < 0.0001 | | | | |
| Insight | 1.411 | 1.241 | 1.604 | < 0.0001 | | | | |
| PSP | 0.963 | 0.951 | 0.976 | < 0.0001 | | | | |
| PANSS total score reduction | 0.976 | 0.966 | 0.987 | < 0.0001 | | | | |
| DAI | 0.816 | 0.750 | 0.888 | < 0.0001 | | | | |
| UKU-psychotic | 1.076 | 0.981 | 1.181 | 0.1220 | | | | |
| UKU-neurological | 1.152 | 0.962 | 1.380 | 0.1243 | | | | |
| UKU-autonomic | 1.151 | 0.979 | 1.352 | 0.0887 | | | | |
| UKU-other | 0.880 | 0.773 | 1.001 | 0.526 | | | | |
| Medication | | | | | | | | |
| Risperidone | | | | | | | | |
| Olanzapine | 1.358 | 0.818 | 2.257 | 0.2370 | | | | |
| Aripiprazole | 0.893 | 0.525 | 1.519 | 0.6775 | | | | |
| Other antipsychotic | 0.662 | 0.090 | 4.886 | 0.6859 | | | | |
| Combination therapy | 4.275 | 0.575 | 31.766 | 0.1557 | | | | |

*Note:* HR = Hazard Ratio. Other abbreviations are explained in the first footnote to Table 1.

face a similar situation, where patients and caregivers are not aware of the need for maintenance treatment and community mental health services are relatively under-developed. A number of non-local patients in participating hospitals were recruited in this study. These patients faced great challenges in coming to follow-up interviews because of travel distance, which may have increased the rate of antipsychotic discontinuation among these participants. However, three of the six centers were located in the north of China, and the other three were located in the south. We attempted to minimize the effects of travel distance with the selection of the participating centers. Finally, several important factors related to treatment continuation, such as family and social support, were not evaluated in the current study.

## 5. Conclusion

The present study showed that approximately half of FES patients discontinued antipsychotics during the first year, which indicates the need for reasonable therapeutic strategies to reduce antipsychotic discontinuation in the early stage of this illness. No specific antipsychotic was found to be better than another. A favorable response to antipsychotic treatment did not indicate good compliance. Clinicians should apply different strategies in the acute and the maintenance phase of schizophrenia treatment to help patients remain on antipsychotic treatment. Greater emphasis should be placed on positive symptom reduction in the acute phase, and a medication switch should be considered for patients without a satisfactory response. Male patients and those with more overall symptoms should receive particular attention for psychoeducation on the need for antipsychotic treatment maintenance to sustain therapeutic benefits; this may be particularly important in developing countries with limited resources and insufficient investment in patient education.

## Acknowledgments

We thank the participating patients and their families, as well as the site investigators, without whom this study would not have been possible. We thank Yangfeng Wu for his help with data analysis. Dr. Xin Yu has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## Funding

This study was supported by the National Key Project of Scientific and Technical Supporting Programs funded by Ministry of Science and Technology of China (no. 2007BAI17B04). The CNFEST received study medications from Eli Lily, Janssen & Janssen and Kanghong Pharmaceutical Co. Ltd. The funding agency of the study and the pharmaceutical companies providing the study medications had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Contributors

XY, YY, FY, ZL, CY, HD and JZ designed the study. XY obtained funding and supervised the study. XZ and ZC analyzed the data. XY, ZC, XZ, YY, YX, CC interpreted the data and drafted the report. ZC, XH, LY, FY, ZL, CW, HD, JZ, YY participated in the collection of data. All authors participated in the critical revision of the report and approved the final report.

## References

Ascher-Svanum, H., Nyhuis, A.W., Stauffer, V., Kinon, B.J., Faries, D.E., Phillips, G.A., Schuh, K., Awad, A.G., Keefe, R., Naber, D., 2010. Reasons for discontinuation and continuation of antipsychotics in the treatment of schizophrenia from patient and clinician perspectives. Curr. Med. Res. Opin. 26 (10), 2403–2410.

Buchanan, R.W., Kreyenbuhl, J., Kelly, D.L., Noel, J.M., Boggs, D.L., Fischer, B.A., Himelhoch, S., Fang, B., Peterson, E., Aquino, P.R., Keller, W., Schizophrenia Patient Outcomes Research Team, 2010. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr. Bull. 36 (1), 71–93.

Correll, C.U., Kishimoto, T., Nielsen, J., Kane, J.M., 2011. Quantifying clinical relevance in the treatment of schizophrenia. Clin. Ther. 33 (12), 24.

Crespo-Facorro, B., de la Foz, V.O., Mata, I., Ayesa-Arriola, R., Suarez-Pinilla, P., Valdizan, E.M., Martinez-Garcia, O., Perez-Iglesias, R., 2014. Treatment of first-episode non-affective psychosis: a randomized comparison of aripiprazole, quetiapine and ziprasidone over 1 year. Psychopharmacology (Berl) 231 (2), 357–366.

Crespo-Facorro, B., Perez-Iglesias, R., Mata, I., Martinez-Garcia, O., Ortiz, V., Pelayo-Teran, J.M., Valdizan, E., Vazquez-Barquero, J.L., 2012. Long-term (3-year) effectiveness of haloperidol, risperidone and olanzapine: results of a randomized, flexible-dose, open-label comparison in first-episode nonaffective psychosis. Psychopharmacology (Berl) 219 (1), 225–233.

Derks, E.M., Fleischhacker, W.W., Boter, H., Peuskens, J., Kahn, R.S., Group, E.S., 2010. Antipsychotic drug treatment in first-episode psychosis: should patients be switched to a different antipsychotic drug after 2, 4, or 6 weeks of nonresponse? J. Clin. Psychopharmacol. 30 (2), 176–180.

Emsley, R., Chiliza, B., Asmal, L., 2013. The evidence for illness progression after relapse in schizophrenia. Schizophr. Res. 148 (1–3), 117–121.

Essock, S.M., Covell, N.H., Davis, S.M., Stroup, T.S., Rosenheck, R.A., Lieberman, J.A., 2006. Effectiveness of switching antipsychotic medications. Am. J. Psychiatry 163 (12), 2090–2095.

Faries, D.E., Ascher-Svanum, H., Nyhuis, A.W., Kinon, B.J., 2008. Switching from risperidone to olanzapine in a one-year, randomized, open-label effectiveness study of schizophrenia. Curr. Med. Res. Opin. 24 (5), 1399–1405.

Gaebel, W., Riesbeck, M., von Wilmsdorff, M., Burns, T., Derks, E.M., Kahn, R.S., Rossler, W., Fleischhacker, W.W., Group, E.S., 2010. Drug attitude as predictor for effectiveness in first-episode schizophrenia: results of an open randomized trial (EUFEST). Eur. Neuropsychopharmacol. 20 (5), 310–316.

Han, X., Yuan, Y.B., Yu, X., Zhao, J.P., Wang, C.Y., Lu, Z., Yang, F.D., Dong, H., Wu, Y.F., Ungvari, G.S., Xiang, Y.T., Chiu, H.F., 2014. The Chinese first-episode schizophrenia trial: background and study design. East Asian Arch. Psychiatry 24 (4), 169–173.

Hogan, T.P., Awad, A.G., Eastwood, R., 1983. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. Psychol. Med. 13 (1), 177–183.

Huang, H.F., Wang, X.L., 2011. A survey of reasons for medication discontinuation in 233 patients with schizophrenia. Med. J. Chin. People's Health 23 (19), 2.

Jung, S.H., Kim, W.H., Choi, H.J., Kang, M.H., Lee, J.S., Bae, J.N., Kim, C.E., 2011. Factors affecting treatment discontinuation and treatment outcome in patients with schizophrenia in Korea: 10-year follow-up study. Psychiatry Investig. 8 (1), 22–29.

Kahn, R.S., Fleischhacker, W.W., Boter, H., Davidson, M., Vergouwe, Y., Keet, I.P., Gheorghe, M.D., Rybakowski, J.K., Galderisi, S., Libiger, J., Hummer, M., Dollfus, S., Lopez-Ibor, J.J., Hranov, L.G., Gaebel, W., Peuskens, J., Lindefors, N., Riecher-Rossler, A., Grobbee, D.E., E.S. Group, 2008. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet 371 (9618), 1085–1097.

Kane, J.M., Kishimoto, T., Correll, C.U., 2013. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. World Psychiatry 12 (3), 216–226.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Landolt, K., Rossler, W., Ajdacic-Gross, V., Derks, E.M., Libiger, J., Kahn, R.S., Fleischhacker, W.W., Eufest Study Group, 2016. Predictors of discontinuation of antipsychotic medication and subsequent outcomes in the European First Episode Schizophrenia Trial (EUFEST). Schizophr. Res. 172 (1–3), 145–151.

Leucht, S., Heres, S., Kissling, W., Davis, W., 2011. Evidence-based pharmacotherapy of schizophrenia. Int. J. Neuropsychopharmacol. 14 (2), 269–284.

Leucht, S., Zhao, J., 2014. Early improvement as a predictor of treatment response and remission in patients with schizophrenia: a pooled, post-hoc analysis from the asenapine development program. J. Psychopharmacol. 28 (4), 387–394.

Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S., Davis, S.M., Davis, C.E., Lebowitz, B.D., Severe, J., Hsiao, J.K., Clinical Antipsychotic Trials of Intervention Effectiveness, Investigators, 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. 353 (12), 1209–1223.

Lingjaerde, O., Ahlfors, U.G., Bech, P., Dencker, S.J., Elgen, K., 1987. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta. Psychiatr. Scand. Suppl. 334, 1–100.

McEvoy, J.P., Lieberman, J.A., Perkins, D.O., Hamer, R.M., Gu, H., Lazarus, A., Sweitzer, D., Olexy, C., Weiden, P., Strakowski, S.D., 2007. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. Am. J. Psychiatry 164 (7), 1050–1060.

Mustafa, S., Joober, R., Lepage, M., Iyer, S., Shah, J., Malla, A., 2018. Predictors of 'all-cause discontinuation' of initial oral antipsychotic medication in first episode psychosis. Schizophr. Res. 201, 287–293.

Perez-Iglesias, R., Crespo-Facorro, B., Martinez-Garcia, O., Ramirez-Bonilla, M.L., Alvarez-Jimenez, M., Pelayo-Teran, J.M., Garcia-Unzueta, M.T., Amado, J.A., Vazquez-Barquero, J.L., 2008. Weight gain induced by haloperidol, risperidone and olanzapine after 1 year: findings of a randomized clinical trial in a drug-naive population. Schizophr. Res. 99 (1-3), 13–22.

Robinson, D.G., Woerner, M.G., Alvir, J.M., Geisler, S., Koreen, A., Sheitman, B., Chakos, M., Mayerhoff, D., Bilder, R., Goldman, R., Lieberman, J.A., 1999a. Predictors of

treatment response from a first episode of schizophrenia or schizoaffective disorder. Am. J. Psychiatry 156 (4), 544–549.
Robinson, D., Woerner, M.G., Alvir, J.M., Bilder, R., Goldman, R., Geisler, S., Koreen, A., Sheitman, B., Chakos, M., Mayerhoff, D., Lieberman, J.A., 1999b. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch. Gen. Psychiatry 56 (3), 241–247.
Samara, M.T., Leucht, C., Leeflang, M.M., Anghelescu, I.G., Chung, Y.C., Crespo-Facorro, B., Elkis, H., Hatta, K., Giegling, I., Kane, J.M., Kayo, M., Lambert, M., Lin, C.H., Moller, H.J., Pelayo-Teran, J.M., Riedel, M., Rujescu, D., Schimmelmann, B.G., Serretti, A., Correll, C.U., Leucht, S., 2015. Early improvement as a predictor of later response to antipsychotics in schizophrenia: a diagnostic test review. Am. J. Psychiatry 172 (7), 617–629.
San, L., Arranz, B., Perez, V., Safont, G., Corripio, I., Ramirez, N., Duenas, R., Alvarez, E., 2012. One-year, randomized, open trial comparing olanzapine, quetiapine, risperidone and ziprasidone effectiveness in antipsychotic-naive patients with a first-episode psychosis. Psychiatry Res. 200 (2–3), 693–701.
Schennach, R., Riesbeck, M., Mayr, A., Seemuller, F., Maier, W., Klingberg, S., Heuser, I., Klosterkotter, J., Gastpar, M., Schmitt, A., Sauer, H., Schneider, F., Jager, M., Wolwer, W., Gaebel, W., Moller, H.J., Riedel, M., 2013. Should early improvement be re-defined to better predict the maintenance of response in first-episode schizophrenia patients? Acta. Psychiatr. Scand. 127 (6), 474–481.
Shu, L. (Ed.), 2007. Guidelines for Prevention and Treatment of Schizophrenia. Peking University Medical Press.
Spearing, M.K., Post, R.M., Leverich, G.S., Brandt, D., Nolen, W., 1997. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res. 73 (3), 159–171.
Tang, W.D., Liu, C.N., 2009. One- year follow up study ofantipsychotics in non - hospitalized patients with first episode schizophrenia. Shanghai Arch. Psychiatry 21 (1), 3.
Tianmei, S., Liang, S., Yun'ai, S., Chenghua, T., Jun, Y., Jia, C., Xueni, L., Qi, L., Yantao, M., Weihua, Z., Hongyan, Z., 2011. The Chinese version of the Personal and Social Performance Scale (PSP): validity and reliability. Psychiatry Res. 185 (1–2), 275–279.
Tiihonen, J., Tanskanen, A., Taipale, H., 2018. 20-year nationwide follow-up study on discontinuation of antipsychotic treatment in first-episode schizophrenia. Am. J. Psychiatry 175 (8), 765–773.
Winton-Brown, T.T., Elanjithara, T., Power, P., Coentre, R., Blanco-Polaina, P., McGuire, P., 2017. Five-fold increased risk of relapse following breaks in antipsychotic treatment of first episode psychosis. Schizophr. Res. 179, 50–56.
Zhu, Y., Li, C., Huhn, M., Rothe, P., Krause, M., Bighelli, I., Schneider-Thoma, J., Leucht, S., 2017. How well do patients with a first episode of schizophrenia respond to antipsychotics: a systematic review and meta-analysis. Eur. Neuropsychopharmacol. 27 (9), 835–844.