Comparison between olanzapine and aripiprazole treatment for 104 weeks after hospital discharge in schizophrenia spectrum disorders: a multicenter retrospective cohort study in a real-world setting

Tomonari Hosokawa[1), 2)], Chikara Miyaji, M.A.[3)], Yusaku Yoshimura M.D., Ph.D.[2)], Kenji Washida, M.D., Ph.D.[2)], Yuji Yada, M.D., Ph.D.[4)], Shinji Sakamoto, M.D., Ph.D. [1)], Yuko Okahisa, M.D., Ph.D. [1)], Soshi Takao, M.D., Ph.D. [3)], Akira Nomura, M.D., Ph.D. [5)], Yoshiki Kishi, M.D. [4)], Toshiki Harada, M.D. [6)], Manabu Takaki, M.D., Ph.D. [1)]*, Toshihiko Takeda, M.D., Ph.D. [2)], and Norihito Yamada, M.D., Ph.D. [1)]

1) Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

2) Department of Psychiatry, Zikei Hospital/Zikei Institute of Psychiatry

3) Department of Epidemiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

4) Okayama Psychiatric Medical Center

5) Momonosato Hospital

6) Taiyo Hills Hospital

*Corresponding author: Manabu Takaki, M.D., Ph.D.

Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

E-mail address: manabuta@cc.okayama-u.ac.jp

Tel.: +81-86-235-7242 Fax: +81-86-235-7246

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Author Contributions

T. Hosokawa, Y. Yoshimura, K. Washida, Y. Yada, S. Sakamoto, Y. Okahisa, S. Takao, A. Nomura, Y. Kishi, T. Harada, M. Takaki, T. Takeda, and N. Yamada participated in the design of the study, supervised the project, and contributed intellectually to the interpretation of the data. T. Hosokawa, Y. Yoshimura, K. Washida, Y. Yada, A. Nomura, Y. Kishi, and T. Harada investigated patient clinical records. C. Miyaji and S. Takao performed the statistical analyses. All authors contributed to and have approved the final manuscript.

Abstract

***Rationale*:** The long-term effectiveness of olanzapine and aripiprazole in real clinical conditions at flexible doses in patients after hospital discharge has not been evaluated yet.

***Objectives*:** This study was a multicenter retrospective cohort study. Patients with schizophrenia (n=398) were prescribed olanzapine (n=303) or aripiprazole (n=95) at hospital discharge. The continuation of olanzapine or aripiprazole at 26, 52, or 104 weeks after the hospital discharge were compared using a Cox proportional hazards model and adjusted for possible confounders.

***Results*:** The Kaplan-Meier survival curves revealed that the continuation of olanzapine at 26 (P=0.001) and 52 weeks (P=0.018) was significantly higher than that of aripiprazole but not at 104 weeks. Olanzapine was better than aripiprazole in efficacy at 26 (hazard ratio: 0.321, 95% confidence interval: 0.159–0.645, P=0.001), 52 (hazard ratio: 0.405, 95% confidence interval: 0.209–0.786, P=0.008), and 104 weeks (hazard ratio: 0.438, 95% confidence interval: 0.246–0.780, P=0.005). Aripiprazole was better than olanzapine in tolerability at 104 weeks (hazard ratio: 4.574, 95% confidence interval: 1.415–14.787, P=0.011). Rates after two years continuation of olanzapine and aripiprazole were not significantly different in patients with less than five years' duration of illness, but olanzapine was more commonly maintained for more than two years in those patients who had been ill for over five years' due to its greater efficacy.

Conclusion: Olanzapine treatment showed better continuation rates at 26 and 52 after hospital discharge than aripiprazole, whereas maintenance with the two antipsychotics did not differ significantly at 104 weeks, due reduced tolerability of long-term olanzapine treatment.

Keywords: schizophrenia, olanzapine, aripiprazole, long-term efficacy, long-term tolerability, Kaplan-Meier, Cox proportional hazards model

Introduction

Schizophrenia is a chronic disorder with a high risk of relapse, and about 80% of patients with schizophrenia experience relapse during the maintenance phase (Robinson et al. 1999; Üçok and Kara 2020). Discontinuation of treatment is associated with a very high risk of relapse after even a single psychotic episode (Üçok and Kara 2020; Emsley et al. 2013). The severity of symptoms is significantly related to the number of relapses (Curson et al. 1985; Emsley et al. 2013), and the decrease in the number of relapses is related to the better treatment response (Emsley et al. 2013; Zhu et al. 2017; Lieberman et al. 1993). Thus, prevention of relapse is very important to maintain better social function and remission in patients with schizophrenia.

Antipsychotics reduce the risk of relapse in patients with schizophrenia (Ceraso et al. 2020; Thompson et al. 2018). Though most international guidelines recommend continuing antipsychotics by schizophrenia patients with multiple relapse episodes (Shimomura et al. 2020), antipsychotics are frequently discontinued. A study of the effectiveness in patients with chronic schizophrenia reported that 74% discontinued their antipsychotics within 18 months (Lieberman et al. 2005), and 42% of patients with a first episode discontinued antipsychotics within 12 months (Kahn et al. 2008). Reasons for the discontinuation of antipsychotics include lack of efficacy, intolerability, and the patient's own decision (Lieberman et al. 2005). In order to achieve continuous treatment with antipsychotics, it is necessary to select appropriate antipsychotics with sufficient efficacy and tolerability for each patient.

Olanzapine (OLZ) and aripiprazole (APZ) are second-generation antipsychotics that are widely used for

the treatment of schizophrenia. A previous meta-analysis indicated that antipsychotics other than clozapine differ in tolerability but not in efficacy (Huhn et al. 2019). In addition, a meta-analysis of maintenance therapy found differences in tolerability, but no differences in relapse prevention among the antipsychotics (Schneider-Thoma et al. 2022). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, OLZ was associated with a longer time to treatment discontinuation due to lack of efficacy and a higher risk of discontinuation owing to intolerability, such as weight gain or metabolic effects, compared to other antipsychotics in patients with chronic schizophrenia (Lieberman et al. 2005). However, there are no studies that have examined the difference in effectiveness of OLZ and APZ beyond 52 weeks in maintenance therapy after the hospital discharge. In addition, are no study comparing the long-term efficacy and tolerability of these two medications in real-world clinical settings and flexible dosing regimens has been reported. Patients with severe acute conditions may be excluded from studies in clinical trials due to a lack of consent.

When evaluating the antipsychotics' effectiveness in clinical practice, comparisons of patients in different phases, such as acute or chronic phase, may be heterogeneous in terms of efficacy, tolerability, and adherence. In addition, switching antipsychotics in patients with chronic schizophrenia is more complicated because the pharmacological profiles of frequently used second-generation antipsychotics are substantially different despite their similarities (Cerovecki et al. 2013), and switching to APZ is especially difficult (Obayashi et al. 2020). The antipsychotics prescribed at the time of hospital discharge are considered to ameliorate the patient's acute symptoms that required the hospitalization and to show an optimal balance of risk and benefit in each patient. By evaluating the rates of antipsychotic continuation from the time of hospital

discharge, it is possible to assess the overall real-world clinical effectiveness in the maintenance after hospital discharge even in patients with different phases of schizophrenia.

The purpose of this study was to identify the long-term effectiveness of OLZ and APZ treatment in a 104-week period after hospital discharge, evaluating both the maintenance dose of these two drugs and the illness duration.

Material and methods

Study design and setting

This study was a multicenter retrospective cohort study. We investigated all patients with schizophrenia treated with OLZ or APZ who were discharged from four psychiatric hospitals in Okayama Prefecture between 2003 and 2012.

Ethical standards

This study was approved by the research Ethics Committees at Zikei Hospital (Reference Number: 168 (3-1)), the Okayama Psychiatric Medical Center (Reference Number: 2021-1), and Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (Reference Number: 2104-014) and followed the principles of the Declaration of Helsinki. The informed assent is shown on the homepage of Zikei Hospital, Okayama Psychiatric Medical Center, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Momonosato Hospital, and Taiyo Hills Hospital.

Population

Patients aged 16 to 65 years who were diagnosed by psychiatrists with schizophrenia spectrum disorder based on the International Classification of Diseases, 10th Edition (ICD-10), were included. All patients treated with OLZ or APZ at the time of hospital discharge were included. The concomitant use of antidepressants, benzodiazepines, mood stabilizers, anticholinergics, and other antipsychotics for sleep at under 25 mg/day chlorpromazine (CP)-equivalent doses (Gardner et al. 2010; Kane et al. 2003) was permitted. Patients were excluded if they changed from the hospital where they were discharged to another, had also been diagnosed with an organic mental disorder, were receiving long-acting injectable antipsychotics, or were prescribed another antipsychotic above 25 mg/day CP-equivalent doses.

Data collection and measurements

The survey data were collected by contacting psychiatrists and retrospectively examining their medical records. We collected information on sociodemographic characteristics, duration of illness, length of hospitalization, OLZ or APZ dosage at hospital discharge, concomitant use of anticholinergic medication, and daily dosage of antipsychotic medications during follow-up. The primary endpoints were the rate and duration of continuation of OLZ or APZ at 26, 52, or 104 weeks after hospital discharge. Discontinuation was defined as (1) a change of antipsychotics from OLZ or APZ or addition of another antipsychotic above the 25 mg/day CP-equivalent dose, (2) hospitalization for psychosis exacerbation, or (3) other reasons such as patient death

or loss to follow-up. In addition, the reasons for the change of antipsychotic or addition of other antipsychotics were categorized as: (1) lack of efficacy (changed by the psychiatrist due to insufficient response, (2) intolerability (changed by the psychiatrist due to poor tolerability), or (3) the patient's own decision (changed at the patient's demand, although the psychiatrist did not recognize the need to change). These measures provide an indicator of overall effectiveness that reflects patient and psychiatrist decisions regarding efficacy and tolerability (Lieberman et al. 2005). Next, we divided patients into low-dose (2.5–10 mg/day of OLZ or 3–15 mg/day of APZ) or high-dose (12.5–30 mg/day of OLZ or 18–30 mg/day of APZ) groups depending on their respective modal doses. The dose range for each medication was delimited by the median modal dose of APZ (18 mg/day), which was then converted to a similar modal dose of OLZ. The modal dose was defined as the most frequent dose of each medication used from hospital discharge to the end of observation. We compared the rates of continuation of OLZ and APZ at low or high dose.

Statistical analysis

The Pearson $\chi 2$ test was used to compare sex, percentage of patients with less than 5 years' duration of illness, percentage of anticholinergic medications in concomitant use, percentage of antipsychotic drugs in concomitant use with less than 25 mg/day CP equivalent dose, and percentage of OLZ or APZ continuation over 2 years. The Mann-Whitney U test was used to compare age at hospital discharge, duration of illness, duration of hospitalization, and OLZ or APZ (CP equivalent) dose at hospital discharge. The cumulative survival percentage of OLZ or APZ was estimated by the Kaplan-Meier method. The log-rank test was used

for univariate comparisons. We adjusted for the following possible confounders in our analysis: sex, age at hospital discharge, duration of illness, duration of hospitalization, baseline dose (CP equivalent dose), concurrent use of anticholinergic drugs, and concurrent use of another antipsychotic for sleep (CP equivalent dose ≤25 mg). Hazard ratios (HR) for the risk of discontinuation of OLZ versus APZ at 26, 52, or 104 weeks after hospital discharge were compared by using a Cox proportional hazards model. The confounders above were used for adjustment. Additionally, hazard ratios for the risk of discontinuation of a low versus high dose of OLZ or APZ were also compared by the same statistical analyses. All statistical analyses were conducted by using STATA 14SE for Windows (Stata Corp., College Station, TX, USA).

Results

Baseline characteristics of patients

A total of 398 patients with schizophrenia spectrum disorder were included in this study. The characteristics of the patients are shown in Table 1. OLZ (n=303) or APZ (n=95) was administered. Median patient age was 36.0 years (interquartile range, 27.9–44.8) with OLZ and 36.7 years (interquartile range, 27.7–47.2) with APZ. Median duration of illness was 6.5 years (interquartile range, 1.5–17.2) with OLZ and 6.1 years (interquartile range, 1.7–11.2) with APZ. The median duration of hospitalization was 12.1 weeks (interquartile range, 5.7–21.4) with OLZ and 8.1 weeks (interquartile range, 2.7–13.6) with APZ, and the two groups were statistically different ($p<0.001$). Median antipsychotic CP equivalent doses at hospital discharge were 600.6 mg/day (interquartile range, 300.3–600.6) for OLZ and 480.0 mg/day (interquartile range, 240.0–

480.0) for APZ, and the two groups were statistically different ($p<0.001$).

Table 2 shows baseline characteristics of patients and continuation rates of antipsychotics at low (n=174) or high dose (n=224). The low-dose group (4.22 (0.97–11.8) years) had a shorter duration of illness than the high-dose group (7.56 (3.05–44.5) years) ($p < 0.001$), and the low-dose group (52.9%) had a higher percentage of under 5 years' duration of illness than the high-dose group (39.3%) (p=0.00932). Concurrent use of anticholinergics was higher in the high-dose group (34.4%) than in the low-dose group (24.1%) (p=0.0355). Continuation rates were significantly higher in the low-dose group (74.7%) than in the high-dose group (64.7%) only at 26 weeks (p=0.0426).

Comparison of olanzapine and aripiprazole treatment maintenance after hospital discharge

The continuation rates of treatment were 42.9% with OLZ and 38.9% with APZ at 104 weeks. The median durations of treatment were 77.4±40.4 weeks with OLZ and 49.6±44.7 weeks with APZ. The discontinuation rates of OLZ were 27.1% at 26 weeks, 39.6% at 52 weeks, and 57.1% at 104 weeks. The discontinuation rates of APZ were 43.2% at 26 weeks, 50.5% at 52 weeks, and 61.1% at 104 weeks.

Figure 1 shows the Kaplan-Meier survival curves at 26, 52, and 104 weeks after hospital discharge. There was no difference between OLZ and APZ treatments in survival duration at 104 weeks. On the other hand, there were significantly longer survival durations with OLZ than APZ at 26 and 52 weeks (log-rank test at 26 weeks: $p = 0.001$, log-rank test at 52 weeks: $p = 0.018$).

Continuation of olanzapine and aripiprazole after hospital discharge, COX proportional hazards model

The risk of OLZ discontinuation was significantly lower than discontinuation of APZ at 26 weeks (HR: 0.518, 95% CI: 0.349–0.767, P=0.001) and 52 weeks (HR: 0.659, 95% CI: 0.466–0.933, P=0.019) in fully adjusted models (Table 3, Supplementary Table 1). There was statistically no difference in the risk of discontinuation at 104 weeks (HR: 0.797, 95% CI: 0.586–1.081, P=0.148).

In the detailed reasons, OLZ showed a lower rate of discontinuation due to lack of efficacy at 26 weeks (HR: 0.321, 95% CI: 0.159–0.645, P=0.001), at 52 weeks (HR: 0.405, 95%CI: 0.209–0.786, P=0.008), and at 104 weeks (HR: 0.438, 95%CI: 0.246–0.780, P=0.005) than APZ. OLZ also showed a lower rate of discontinuation due to hospitalization for psychosis exacerbation at 26 weeks (HR: 0.451, 95% CI: 0.232–0.878, P=0.019) and patient decision at 52 weeks (HR: 0.267, 95% CI: 0.086–0.824, P=0.022) than APZ. On the other hand, OLZ showed a higher risk of discontinuation due to intolerability at 104 weeks (HR: 4.574, 95% CI, 1.415–14.787, P=0.011) than APZ.

Olanzapine and aripiprazole maintenance treatments according to the duration of illness

Patients with under 5 years' duration of illness were administered a significantly lower dose of OLZ (average 10 mg/day) than those with over 5 years' duration of illness (average 20 mg /day) (p>0.00875). (Table 4). APZ showed a similar tendency (average 18 mg/day, under 5 years vs. average 24 mg/day, over 5 years: p>0.101).

In patients with under 5 years' duration of illness, the discontinuation of OLZ and APZ due to any

reason was not statistically different at 26, 52, and 104 weeks. In detail, OLZ showed a lower risk of discontinuation due to a lack of efficacy at 26 weeks (HR: 0.232, 95% CI: 0.068–0.795, P = 0.020), and a higher risk of discontinuation due to intolerability at 104 weeks (HR: 3.728, 95% CI: 1.114–12.470, P = 0.033) than APZ.

In patients with over 5 years' duration of illness, OLZ showed lower risks of discontinuation for any reason at 26 weeks (HR: 0.441, 95% CI: 0.263–0.738, P=0.002), at 52 weeks (HR: 0.559, 95% CI: 0.355-0.880, P=0.012), and at 104 weeks (HR: 0.568, 95% CI: 0.380–0.849, P = 0.006) than APZ. In detail, OLZ showed a lower risk of discontinuation due to hospitalization for psychotic exacerbations at 26 weeks (HR: 0.359, 95% CI: 0.164–0.785, P = 0.010), due to the patient's own decision at 52 weeks (HR: 0.045, 95% CI: 0.004–0.465, P = 0.009) and at 104 weeks (HR: 0.045, 95% CI: 0.004–0.465, P = 0.009), and due to lack of efficacy at 104 weeks (HR: 0.408, 95% CI: 0.200–0.832, P = 0.014) than APZ. OLZ (19/167: 11.4%) was not used continuously due to intolerability at 104 weeks, but intolerability of APZ was not reported (0/51: 0%).

Olanzapine and aripiprazole maintenance treatments at low and high doses

The median modal dose at 104 weeks after discharge was 15 mg/day for OLZ and 18 mg/day for APZ (Supplementary Table 2). The duration of illness for patients in high-dose groups of the two medications was longer for OLZ (9.42 years: 3.16–19.04) than for APZ (5.88 years: 2.85–8.72) (P = 0.0223). On the other hand, there was no significant difference in the duration of illness in patients in low-dose groups of the two medications (OLZ 4.08 years (0.96–11.02) vs. APZ 6.05 years (1.16–18.05); P = 0.708).

In fully adjusted models, high-dose OLZ (12.5–30 mg/day: n = 170) showed a significantly lower risk of discontinuation for any reason than high-dose APZ (15–30 mg/day: n = 54) only at 26 weeks (HR: 0.538, 95% CI: 0.313–0.924, P=0.024). There was statistically no difference in the risk of discontinuation at 52 and 104 weeks. Low-dose OLZ (2.5–10 mg/day: n = 133) and low-dose APZ (3–15 mg/day: n = 41) were not significantly different in rates of discontinuation for any reason at 26, 52, and 104 weeks.

Discussion

This is the first study showing that the continuation rate of OLZ by patients with schizophrenia spectrum disorder was significantly higher than that of APZ at 26 and 52 weeks after hospital discharge, but not at 104 weeks. OLZ was better than APZ in efficacy at 26, 52, and 104 weeks and prevention of hospitalization at 26 and 52 weeks. APZ was better than OLZ in tolerability at 104 weeks.

A previous 28-week study of 566 U.S. in- or out-patient schizophrenia patients showed that the continuations of OLZ and APZ due to all reasons were not significantly different, but discontinuation due to the lack of efficacy of OLZ was significantly lower, and discontinuation due to intolerability, such as weight gain, increased blood glucose levels, and worsening lipid parameters due to OLZ, was higher than APZ (Kane et al. 2009). A 52-week study of 214 U.S., Czech, Polish, Russian, and Ukrainian acute or stable schizophrenia patients (Chrzanowski et al. 2006) and a 26-week study of 317 U.S. schizophrenia patients with acute relapses requiring hospitalization showed similar efficacies but a high risk of weight gain with OLZ (McQuade et al. 2004). In one meta-analysis, the efficacies of OLZ and APZ were almost identical (Huhn et al. 2019), and OLZ

was strongly associated with adverse glyco-metabolic effects while APZ was weakly associated with them (Carnovale et al. 2021; Pillinger et al. 2020). Weight gain with OLZ was not dose-dependent (Jain et al. 2006), and the risk increased over time from the start of OLZ (Bak et al. 2014).

The difference in efficacy between OLZ and APZ appeared earlier than that of intolerability in this study. One reason is that this study assessed the continuation of OLZ and APZ from the time after hospital discharge, and this is different from previous clinical trials. In general, the diet of inpatients is nutritionally controlled, and since dietary and nutritional interventions have been shown to be effective in preventing weight gain and counteracting weight gain in patients with schizophrenia on antipsychotics, weight gain in inpatients under dietary control is thought to be under control (Dayabandara et al. 2017; Faulkner et al. 2007; Teasdale et al. 2017). Besides, weight gain during OLZ treatment may increase over time (Bak et al. 2014), and a high risk of weight gain during OLZ treatment may appear after clinical trials. In addition, the efficacy may be objectively recognized by the attending physicians and be apparent earlier, while weight gain may be subjectively observed by the patient and be apparent later. The next reason is that OLZ has a better continuation rate due to prevention of hospitalization than APZ in high doses at an early stage. The patients taking a high dose of OLZ have a longer duration of illness than those taking a high dose of APZ. Though we didn't investigate the severity of illness in this study, the duration of illness is reported to be related to its severity (Buoli et al. 2012; Becarevic et al. 2022). In analyses of the response to different doses of antipsychotics in acute schizophrenia, OLZ is effective even at higher doses (Meltzer et al. 2008; Kinon et al. 2008; Bobes et al. 2007), whereas APZ reaches a 95% effective dose (ED95) at about 12 mg/day and its efficacy may not increase

at higher doses (Leucht et al. 2020).

Two-year continuation rates of OLZ and APZ in patients were not significantly different in patients with less than 5 years' duration of illness, and the superiority of APZ on the point of tolerability appeared at 104 weeks in this study. Because first-episode schizophrenia patients respond well to antipsychotics (Zhu et al. 2017), the difference in efficacy between OLZ and APZ may not be significant in this study. In terms of intolerability, patients with a shorter duration of illness tend to be more sensitive to the side effects of antipsychotics, such as extrapyramidal symptoms (Kasper 1999), but extrapyramidal symptoms may be improved relatively until hospital discharge in this study. Weight gain is induced even by a low dose of OLZ (Jain et al. 2006) in younger and first-episode patients (Álvarez-Jiménez et al. 2008). Because patients with less than 5 years' duration of illness were administered a low dose of antipsychotics, weight gain may influence the results more than extrapyramidal symptoms. On the other hand, OLZ showed a better continuation rate in patients over five years' duration of illness due to its efficacy. Chronic patients respond poorly to antipsychotics (Stern et al. 1993; Furukawa et al. 2015). Because patients with over five years' duration of illness were administered a high dose of antipsychotics, OLZ may show the better efficacy, even at high doses, than APZ.

There are several limitations to this study. Because it is a retrospective observational study, the results should be confirmed by a prospective study. Other important covariates, such as the severity of symptoms scored by clinical scales, history of electroconvulsive therapy, the number of hospitalizations, and compliance to antipsychotic regimes, were not evaluated. With OLZ, the duration of hospitalization was longer, the CP equivalent dose of antipsychotics at hospital discharge was higher, and the optimal dose was higher

than that of APZ. The highest CP equivalent dose (30 mg/day) of OLZ was higher than that of APZ, because OLZ is usually prescribed at up to 30 mg/day in Japan, although the authorized dose of OLZ is up to 20 mg/day. In addition, fewer patients are prescribed APZ than OLZ. Though the concurrent use of antipsychotics at less than 25 mg/day was under 10%, OLZ and APZ are not purely limited to monotherapy. For future accurate evaluation, it is necessary to increase the number of cases of APZ and to consider other important covariates. However, the present long-term observation in a real-world setting allows us to comprehensively evaluate both the efficacy of clinical treatments and the course of schizophrenia disorders.

OLZ treatment showed better continuation rates at 26 and 52 weeks after hospital discharge in comparison with APZ, whereas the maintenance of the two antipsychotic treatments did not significantly differ at 104 weeks, probably due the reduced tolerability of long-term OLZ treatment. In patients with a shorter duration of illness, APZ might be preferred to OLZ for tolerability. Psychiatrists should select the type and dose of antipsychotics for each patient with consideration of the different characteristics of antipsychotics.

References

Álvarez-Jiménez M, González-Blanch C, Crespo-Facorro B et al. (2008) Antipsychotic-induced weight gain in chronic and first-episode psychotic disorders: a systematic critical reappraisal. CNS Drugs 22:547–562. https://doi.org/https://doi.org/10.2165/00023210-200822070-00002

Bak M, Fransen A, Janssen J et al. (2014) Almost all antipsychotics result in weight gain: a meta-analysis. PLoS One 9:e94112. https://doi.org/10.1371/JOURNAL.PONE.0094112

Bećarević N, Softić R, Osmanović E (2022) Does the duration of the illness affect the severity of negative symptoms of schizophrenia? Mater Sociomed 34:25–27. https://doi.org/10.5455/MSM.2022.33.25-27

Bobes J, Garcia-Portilla MP, Bascaran MT, Saiz PA BM (2007) Quality of life in schizophrenic patients. Dialogues Clin Neurosci 9:215–226. https://doi.org/10.31887/DCNS.2007.9.2/JBOBES

Buoli M, Caldiroli A, Panza G, Altamura AC (2012) Prominent clinical dimension, duration of illness and treatment response in schizophrenia: a naturalistic study. Psychiatry Investig 9:354–360. https://doi.org/10.4306/PI.2012.9.4.354

Carnovale C, Lucenteforte E, Battini V et al. (2021) Association between the glyco-metabolic adverse effects of antipsychotic drugs and their chemical and pharmacological profile: a network meta-analysis and regression. Psychol Med 24:1–13. https://doi.org/10.1017/S0033291721000180

Ceraso A, Lin JJ, Schneider-Thoma J et al. (2020) Maintenance treatment with antipsychotic drugs for schizophrenia. Cochrane database Syst Rev 8:CD008016.

https://doi.org/https://doi.org/10.1002/14651858.CD008016.pub3

Cerovecki A, Musil R, Klimke A et al. (2013) Withdrawal symptoms and rebound syndromes associated with switching and discontinuing atypical antipsychotics: theoretical background and practical recommendations. CNS Drugs 27:545–572. https://doi.org/https://doi.org/10.1007/s40263-013-0079-5

Chrzanowski WK, Marcus RN, Torbeyns A et al. (2006) Effectiveness of long-term aripiprazole therapy in patients with acutely relapsing or chronic, stable schizophrenia: a 52-week, open-label comparison with olanzapine. Psychopharmacology (Berl) 189:259–266. https://doi.org/https://doi.org/10.1007/s00213-006-0564-3

Curson DA, Barnes TR, Bamber RW et al. (1985) Long-term depot maintenance of chronic schizophrenic out-patients: the seven year follow-up of the Medical Research Council fluphenazine/placebo trial. III. Relapse postponement or relapse prevention? The implications for long-term outcome. Br J Psychiatry 146:474–480. https://doi.org/https://doi.org/10.1192/bjp.146.5.474

Dayabandara M, Hanwella R, Ratnatunga S et al. (2017) Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. Neuropsychiatr Dis Treat 13:2231–2241. https://doi.org/https://doi.org/10.2147/NDT.S113099

Emsley R, Chiliza B, Asmal L (2013) The evidence for illness progression after relapse in schizophrenia. Schizophr Res 148:117–121. https://doi.org/https://doi.org/10.1016/j.schres.2013.05.016

Emsley R, Chiliza B, Asmal L, Harvey BH (2013) The nature of relapse in schizophrenia. BMC Psychiatry 13:50. https://doi.org/https://doi.org/10.1186/1471-244X-13-50

Emsley R, Oosthuizen P, Koen L et al. (2013) Comparison of treatment response in second-episode versus first-episode schizophrenia. J Clin Psychopharmacol 33:80–83. https://doi.org/https://doi.org/10.1097/JCP.0b013e31827bfcc1

Faulkner G, Cohn T, Remington G (2007) Interventions to reduce weight gain in schizophrenia. Cochrane Database Syst Rev 1:CD005148. https://doi.org/https://doi.org/10.1002/14651858.CD005148.pub2

Furukawa TA, Levine SZ, Tanaka S et al. (2015) Initial severity of schizophrenia and efficacy of antipsychotics: participant-level meta-analysis of 6 placebo-controlled studies. JAMA psychiatry 72:14—21. https://doi.org/https://doi.org/10.1001/jamapsychiatry.2014.2127

Gardner DM, Murphy AL, O'Donnell H et al. (2010) International consensus study of antipsychotic dosing. Am J Psychiatry 167:686–693. https://doi.org/https://doi.org/10.1176/appi.ajp.2009.09060802

Huhn M, Nikolakopoulou A, Schneider-Thoma J et al. (2019) Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet (London, England) 394:939–951. https://doi.org/https://doi.org/10.1016/S0140-6736(19)31135-3

Jain S, Bhargava M, Gautam S (2006) Weight gain with olanzapine: Drug, gender or age? Indian J Psychiatry 48:39–42. https://doi.org/https://doi.org/10.4103/0019-5545.31617

Kahn RS, Fleischhacker WW, Boter H et al. (2008) Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet (London,

England) 371:1085–1097. https://doi.org/https://doi.org/10.1016/S0140-6736(08)60486-9

Kane JM, Leucht S, Carpenter D, Docherty JP (2003) The expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders. Introduction: methods, commentary, and summary. J Clin Psychiatry 64:5–19. Retrieved from https://www.psychiatrist.com/jcp/

Kane JM, Osuntokun O, Kryzhanovskaya LA et al. (2009) A 28-week, randomized, double-blind study of olanzapine versus aripiprazole in the treatment of schizophrenia. J Clin Psychiatry 70:572–581. https://doi.org/https://doi.org/10.4088/jcp.08m04421

Kasper S (1999) First-episode schizophrenia: the importance of early intervention and subjective tolerability. J Clin Psychiatry 60:5–9. Retrieved from https://www.psychiatrist.com/jcp/

Kinon BJ, Volavka J, Stauffer V et al. (2008) Standard and higher dose of olanzapine in patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, fixed-dose study. J Clin Psychopharmacol 28:392–400. https://doi.org/10.1097/jcp.0b013e31817e63a5

Leucht S, Crippa A, Siafis S et al. (2020) Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia. Am J Psychiatry 177:342–353. https://doi.org/https://doi.org/10.1176/appi.ajp.2019.19010034

Lieberman JA, Stroup TS, McEvoy JP et al. (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353:1209–1223. https://doi.org/https://doi.org/10.1056/NEJMoa051688

Lieberman J, Jody D, Geisler S et al. (1993) Time course and biologic correlates of treatment

response in first-episode schizophrenia. Arch Gen Psychiatry 50:369–376. https://doi.org/https://doi.org/10.1001/archpsyc.1993.01820170047006

McQuade RD, Stock E, Marcus R et al. (2004) A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. J Clin Psychiatry 65:47–56. Retrieved from https://www.psychiatrist.com/jcp/

Meltzer HY, Bobo W V., Roy A et al. (2008) A randomized, double-blind comparison of clozapine and high-dose olanzapine in treatment-resistant patients with schizophrenia. J Clin Psychiatry 69:274–285. https://doi.org/https://doi.org/10.4088/jcp.v69n0214

Obayashi Y, Mitsui S, Sakamoto S et al. (2020) Switching strategies for antipsychotic monotherapy in schizophrenia: a multi-center cohort study of aripiprazole. Psychopharmacology (Berl) 237:167–175. https://doi.org/https://doi.org/10.1007/s00213-019-05352-7

Pillinger T, McCutcheon RA, Vano L et al. (2020) Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. The Lancet Psychiatry 7:64–77. https://doi.org/https://doi.org/10.1016/S2215-0366(19)30416-X

Robinson D, Woerner MG, Alvir JMJ et al. (1999) Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 56:241–247. https://doi.org/https://doi.org/10.1001/archpsyc.56.3.241

Schneider-Thoma J, Chalkou K, Dörries C et al. (2022) Comparative efficacy and tolerability of 32

oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. Lancet (London, England) 399:824–836. https://doi.org/https://doi.org/10.1016/S0140-6736(21)01997-8

Shimomura Y, Kikuchi Y, Suzuki T et al. (2020) Antipsychotic treatment in the maintenance phase of schizophrenia: An updated systematic review of the guidelines and algorithms. Schizophr Res 215:8–16. https://doi.org/https://doi.org/10.1016/j.schres.2019.09.013

Stern RG, Kahn RS DM (1993) Predictors of response to neuroleptic treatment in schizophrenia. Psychiatr Clin North Am 16:313–338. https://doi.org/10.1016/S0193-953X(18)30176-X

Teasdale SB, Ward PB, Rosenbaum S et al. (2017) Solving a weighty problem: systematic review and meta-analysis of nutrition interventions in severe mental illness. Br J Psychiatry 210:110–118. https://doi.org/https://doi.org/10.1192/bjp.bp.115.177139

Thompson A, Winsper C, Marwaha S et al. (2018) Maintenance antipsychotic treatment versus discontinuation strategies following remission from first episode psychosis: systematic review. BJPsych open 4:215–225. https://doi.org/https://doi.org/10.1192/bjo.2018.17

Üçok A, Kara İA (2020) Relapse rates following antipsychotic discontinuation in the maintenance phase after first-episode of schizophrenia: Results of a long-term follow-up study. Schizophr Res 225:31–38. https://doi.org/https://doi.org/10.1016/j.schres.2019.10.015

Zhu Y, Li C, Huhn M et al. (2017) How well do patients with a first episode of schizophrenia respond to antipsychotics: A systematic review and meta-analysis. Eur Neuropsychopharmacol 27:835–844.

https://doi.org/https://doi.org/10.1016/j.euroneuro.2017.06.011

Table 1. Baseline characteristics of patients by OLZ or APZ treatment

	OLZ (n=303)	APZ (n=95)	*P* value
Male sex (n/%)	167 (55.1)	53 (55.8)	0.908*****
Age at discharge (years)	36.0 (27.9 - 44.8)	36.7 (27.7 - 47.2)	0.581******
Age at onset (years)	24.4 (19.3 - 31.3)	27.6 (19.5 - 36.4)	0.0898**
Duration of illness (years)	6.5 (1.5 - 17.2)	6.1 (1.7 - 11.2)	0.301******
5 years or less (n/%)	136 (44.9)	44 (46.3)	0.807*****
Duration of hospitalization (weeks)	**12.1 (5.70 - 21.4)**	**8.1 (2.7 - 13.6)**	**<0.001****
Antipsychotics CP equivalent dose at discharge (mg/day)	**600.6 (300.3 - 600.6)**	**480.0 (240.0 - 480.0)**	**<0.001****
Concurrent use of anticholinergic medications (n/%)	90 (29.7)	29.0 (30.5)	0.878*****
Concurrent use of another antipsychotic for sleep (CP equivalent dose ≤25 mg) (n/%)	24 (7.9)	9 (9.5)	0.632*****

*****χ2 test, ******U test, OLZ olanzapine, APZ aripiprazole, CP chlorpromazine

Table 2. Baseline characteristics of patients and continuation rates of antipsychotics at low or high dose

	Low dose (n=174)	High dose (n=224)	*P* value
Male sex (n/%)	91 (52.3)	129 (57.6)	0.341*****
Age at discharge (years)	36.0 (26.6 - 47.2)	36.2 (28.5 - 44.4)	0.977******
Duration of illness (years)	**4.22 (0.97 - 11.8)**	**7.56 (3.05 - 44.5)**	**<0.001****
5 years or less (n/%)	**92 (52.9)**	**88 (39.3)**	**0.00932***
Duration of hospitalization (weeks)	9.21 (4.14 - 17.2)	11.6 (5.54 - 21.3)	0.0673******
Antipsychotics CP equivalent dose at discharge (mg/day)	300.3 (225.2 - 431.7)	600.6 (480.0 - 600.6)	-
Concurrent use of anticholinergic medications (n/%)	**42 (24.1)**	**77 (34.4)**	**0.0355***
Concurrent use of another antipsychotic for sleep (CP equivalent dose ≤25 mg) (n/%)	11 (6.32)	22 (9.82)	0.283*****
Continuation rate at 26 weeks (%)	**74.7**	**64.7**	**0.0426***
Continuation rate at 52 weeks (%)	62.1	54.5	0.155*
Continuation rate at 104 weeks (%)	46	32.1	0.184*

*****χ2 test, ******U test, OLZ olanzapine, APZ aripiprazole, CP chlorpromazine

OLZ low dose: 2.5-10 mg/day, high-dose: above 12.5-30 mg/day

APZ low dose: 3-15 mg/day, high-dose: above 18-30 mg/day

Table 3. Comparison of OLZ and APZ treatment divided by reasons for discontinuation and hospitalization (Cox proportional hazards model)

	Observation period of 26 weeks						Observation period of 52 weeks						Observation period of 104 weeks					
	Crude model			Fully adjusted model			Crude model			Fully adjusted model			Crude model			Fully adjusted model		
	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value
OLZ vs. APZ																		
Treatment discontinuation																		
For any reason	**0.547**	**0.376 - 0.796**	**0.002**	**0.518**	**0.349 - 0.767**	**0.001**	**0.670**	**0.479 - 0.936**	**0.019**	**0.659**	**0.466 - 0.933**	**0.019**	0.803	0.596 - 1.080	0.148	0.797	0.586 - 1.084	0.148
Lack of efficacy	**0.352**	**0.182 - 0.679**	**0.002**	**0.321**	**0.159 - 0.645**	**0.001**	**0.417**	**0.222 - 0.786**	**0.007**	**0.405**	**0.209 - 0.786**	**0.008**	**0.486**	**0.280 - 0.842**	**0.010**	**0.438**	**0.246 - 0.780**	**0.005**
Intolerability	1.688	0.500 - 5.707	0.399	2.082	0.606 - 7.153	0.244	2.791	0.855 - 9.117	0.089	3.025	0.917 - 9.981	0.069	**4.042**	**1.257 - 12.996**	**0.019**	**4.574**	**1.415 - 14.787**	**0.011**
Patient decision	0.538	0.098 - 2.936	0.474	0.470	0.077 - 2.860	0.412	**0.224**	**0.075 - 0.667**	**0.007**	**0.267**	**0.086 - 0.824**	**0.022**	**0.338**	**0.126 - 0.906**	**0.031**	0.389	0.140 - 1.081	0.070
Hospitalization for psychosis exacerbation	**0.524**	**0.281 - 0.978**	**0.042**	**0.451**	**0.232 - 0.878**	**0.019**	0.780	0.434 - 1.401	0.405	0.701	0.378 - 1.297	0.258	0.925	0.547 - 1.564	0.772	0.840	0.486 - 1.452	0.532
For other reasons	0.552	0.188 - 1.615	0.278	0.515	0.162 - 1.638	0.261	0.538	0.217 - 1.334	0.181	0.581	0.219 - 1.540	0.275	0.563	0.265 - 1.197	0.136	0.624	0.281 - 1.389	0.248

OLZ olanzapine, *APZ* aripiprazole, *CI* confidence interval, *HR* hazard ratio, *CP* chlorpromazine

Fully adjusted model: adjusted by sex, age at discharge, duration of illness, duration of hospitalization, baseline CP equivalent dose (mg/day), concurrent use of anticholinergic drugs, concurrent use of another antipsychotic for sleep (CP equivalent dose ≤25 mg)

Table 4. Comparison between OLZ and APZ treatment divided by duration of illness (Cox proportional hazards model)

A.≤ 5-year duration of illness (n=180）

	Observation period of 26 weeks						Observation period of 52 weeks						Observation period of 104 weeks					
	Crude model			Fully adjusted model			Crude model			Fully adjusted model			Crude model			Fully adjusted model		
	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value
OLZ vs. APZ																		
Treatment discontinuation																		
For any reason	0.678	0.377 to 1.219	0.194	0.762	0.412 to 1.409	0.387	0.798	0.472 to 1.349	0.399	0.932	0.542 to 1.604	0.800	1.130	0.705 to 1.810	0.612	1.368	0.842 to 2.224	0.206
Lack of efficacy	**0.257**	**0.086 to 0.765**	**0.015**	**0.232**	**0.068 to 0.795**	**0.020**	**0.341**	**0.124 to 0.940**	**0.037**	0.355	0.121 to 1.044	0.060	0.529	0.208 to 1.346	0.182	0.517	0.191 to 1.394	0.192
Intolerability	1.250	0.356 to 4.387	0.728	1.645	0.459 to 5.887	0.444	1.820	0.539 to 6.151	0.335	2.234	0.650 to 7.684	0.202	2.677	0.812 to 8.827	0.106	**3.728**	**1.114 to 12.470**	**0.033**
Patient decision	0.886	0.092 to 8.520	0.917	1.046	0.085 to 12.890	0.972	0.726	0.141 to 3.744	0.702	1.001	0.184 to 5.451	0.999	1.214	0.258 to 5.722	0.806	1.833	0.370 to 9.079	0.458
Hospitalization for psychosis exacerbation	1.067	0.298 to 3.825	0.921	1.039	0.273 to 3.945	0.956	1.547	0.451 to 5.309	0.488	1.707	0.483 to 6.036	0.407	1.634	0.627 to 4.259	0.315	1.804	0.674 to 4.827	0.240
For other reasons	0.591	0.108 to 3.227	0.544	0.823	0.130 to 5.211	0.836	0.294	0.074 to 1.176	0.084	0.392	0.084 to 1.826	0.233	0.497	0.162 to 1.521	0.220	0.658	0.195 to 2.219	0.500

B. >5-year duration of illness (n=218)

	Observation period of 26 weeks						Observation period of 52 weeks						Observation periods of 104 weeks					
	Crude model			Fully adjusted model			Crude model			Fully adjusted model			Crude model			Fully adjusted model		
	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value
OLZ vs. APZ																		
Treatment discontinuation																		
For any reason	**0.469**	**0.288 - 0.766**	**0.002**	**0.441**	**0.263 - 0.738**	**0.002**	**0.585**	**0.378 - 0.904**	**0.016**	**0.559**	**0.355 - 0.880**	**0.012**	**0.617**	**0.419 - 0.907**	**0.014**	**0.568**	**0.380 - 0.849**	**0.006**
Lack of efficacy	**0.423**	**0.183 - 0.977**	**0.044**	0.428	0.179 - 1.025	0.057	0.475	0.210 - 1.076	0.074	0.481	0.206 - 1.126	0.092	**0.445**	**0.225 - 0.880**	**0.020**	**0.408**	**0.200 - 0.832**	**0.014**
Intolerability	na			na			na			na			na			na		
Patient decision	0.252	0.016 - 4.042	0.330	0.064	0.001 - 2.850	0.156	**0.047**	**0.005 - 0.403**	**0.005**	**0.045**	**0.004 - 0.465**	**0.009**	**0.047**	**0.005 - 0.403**	**0.005**	**0.045**	**0.004 - 0.465**	**0.009**
Hospitalization for psychosis exacerbation	**0.380**	**0.183 - 0.790**	**0.010**	**0.359**	**0.164 - 0.785**	**0.010**	0.570	0.290 - 1.121	0.104	0.555	0.271 - 1.136	0.107	0.663	0.351 - 1.250	0.204	0.590	0.302 - 1.152	0.122
Other reasons	0.523	0.131 - 2.095	0.360	0.387	0.085 - 1.760	0.219	0.830	0.228 - 3.019	0.777	0.659	0.168 - 2.582	0.550	0.622	0.221 - 1.747	0.367	0.535	0.181 - 1.578	0.257

OLZ olanzapine, *APZ* aripiprazole, *CI* confidence interval, *HR* hazard ratio, *CP* chlorpromazine

Fully adjusted model: adjusted by sex, age at discharge, duration of hospitalization, baseline CP equivalent dose (mg/day), concurrent use of anticholinergic drugs, concurrent use of another antipsychotic for sleep (CP equivalent dose ≤25 mg)

'na' denotes not available: No patient discontinued APZ due to intolerability.

Figure 1. Kaplan-Meier survival curves at 26, 52, and 104 weeks after discharge