Comparative effectiveness of second generation long-acting injectable antipsychotics based on nationwide database research in Hungary: an update

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Conflicts of Interest:

PK, VT, and LF are employees of Janssen and may own stock or stock options. PT was formerly an employee of Janssen and may own stock or stock options. TB, RH are employees of Healthware Ltd. An organization which was contracted and paid by Janssen for data acquisition and analysis. IB reports grants from Acadia, European Group for Research in Schizophrenia, Janssen, Lundbeck and Gedeon Richter and personal fees (consultation and/or speaker fee) from Angelini, Gedeon Richter, Janssen/Janssen Cilag, Sun Pharma, outside the submitted work over the last three years. PC reports no conflict of interest.

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Informed consent: Not applicable.

Abstract

Greater 1-year and 2-year treatment continuation rates and longer median time to discontinuation for second-generation antipsychotic (SGA) long-acting injectables (LAIs) vs. oral antipsychotics (OAPs) in Hungary were previously reported. This study reports an updated comparison between new LAIs vs OAPs in Hungary. De-identified claims data from Hungarian National Health Insurance Fund database of schizophrenia patients who were newly initiated on SGAs (November 01, 2016 to June 30, 2017) were retrospectively analyzed. Primary outcomes were likelihood of all-cause 1-year and 1.5-year discontinuation of newly initiated SGA and median time till discontinuation. Among 5,400 patients, 3,977 (73.6%) were OAP users and 1,423 (26.4%) were LAI users. The 1-year continuation rate were 12.7% (risperidone)–34.1% (olanzapine) for OAPs and 26.4% (risperidone LAI)–78.6% (paliperidone 3-monthly [PP3M]) for LAIs. The 1.5-year continuation rates were 9.3%–29.5% for OAPs and 24.9%–76.4% for LAIs. Median (95% CI) time to discontinuation was 52 (33–67) days (clozapine)–152 (134–168) days (aripiprazole) for OAPs and 125 (64–196) days (risperidone LAI)–491 (250–not reached) days (aripiprazole LAI) for LAIs. All-cause discontinuation risk was significantly higher in all OAPs vs. PP3M and aripiprazole LAI ($P<0.01$) as well as in each LAI vs. PP3M ($P<0.05$). Patients switching on new LAIs from another LAI remained longer than those who switched from OAPs/no previous treatment. Results showed the advantage of LAIs over OAPs in terms of time to treatment discontinuation. Moreover, new SGA LAIs (PP3M) seem to be better than previous LAIs in terms of time to treatment discontinuation.

Keywords: Long acting injectables, Oral antipsychotics, Schizophrenia, Second-generation antipsychotic

Introduction

Schizophrenia, in the majority of afflicted people, is a severe and devastating mental disorder characterized by disruptions in the sense of self, perception, thinking, and language.[1] The detrimental effects of schizophrenia include decline of cognitive functions[2] and impairments in daily activities, social functioning, and work productivity[3]; it also negatively impacts patients, caregivers, and society. Although antipsychotics are the mainstay of management of schizophrenia,[4] the effectiveness of antipsychotics is strongly associated with medication adherence.[5] Unfortunately, partial compliance with the prescribed antipsychotics regimen is common in patients with schizophrenia.[1, 6]

Usage of long-acting injectable (LAI) antipsychotics in the real world has been reported to lead to greater medication adherence compared with oral antipsychotics (OAPs) resulting in fewer hospitalizations and lower overall healthcare costs.[7-11] We have previously reported the results of a similar analysis which analyzed data from the Hungarian National Health Insurance Fund database (NHIF).[12] This study was conducted as part of a larger project named ATTILA (Antipsychotic Treatment with Injectable Long-Acting Antipsychotics in Hungary). In this study, 1-year and 2-year treatment continuation rates were reported to be greater for second-generation antipsychotic (SGA) LAIs compared with OAPs (32%–64% vs. 17%–31% and 17%–52% vs. 10%–22%, respectively). Moreover, the median time to discontinuation was longer for LAIs than OAPs.

Since the publication of the aforementioned study, the treatment landscape for schizophrenia in Hungary has changed with the introduction of new LAIs such as long-acting aripiprazole and long-acting paliperidone 3-monthly formulation. This gave us the opportunity to analyze the effect of change in treatment options on overall discontinuation of antipsychotics, using a similar methodology as our previous study.[12] The present study's objective was to perform a full population comparison between LAIs and oral formulations of

SGAs using a follow-up period up to 1.5 years. The analysis was performed after receiving ethical approval from the Committee of Science and Research Ethics of the Medical Research Council, approval number 30175-2/2018/EKU dated May 30, 2018.

Methods

Data source

De-identified records were obtained from the longitudinal, nationwide database of the Hungarian NHIF. This database contains detailed healthcare service records for the whole population of Hungary and is linked to the social security number, a unique patient identifier that enables longitudinal patient pathway analysis. The database includes patient-level demographic data as well as inpatient, outpatient, and prescription drug data.

The NHIF handles patient data based on law (*Act No. 80/1997 on mandatory health insurance* coverage) and data access is provided for real-world analyses (based on *Act 63/2012 on the re-use of public data*). Only NHIF had direct access to patient level data; other parties could only access the data indirectly through NHIF as per NHIF's data privacy regulations. Due to this regulation and the retrospective nature of the study, patient level consent was not required for the analysis.

Study population

The study population was similar to our previous analysis.[12] Briefly, patients who started a new treatment during the inclusion period (November 01, 2016 to June 30, 2017) of any SGA as monotherapy among oral amisulpride (AMIS), oral aripiprazole monohydrate (ARIP), oral clozapine (CLOZ), oral olanzapine (OLAN), oral quetiapine (QUET), oral risperidone (RISP), oral paliperidone (PALI), risperidone long-acting injection (RLAI), olanzapine long-acting injection (OLAI), aripiprazole long-acting (ALAI), paliperidone long-acting injection 1 monthly (PP1M), and paliperidone long-acting injection 3 monthly (PP3M) were included in the study. The date of the first dispensation of the new antipsychotic during

the inclusion period was considered as the index date. At least one documented schizophrenia diagnosis (F20.0–F20.9) according to ICD-10 (International Classification of Diseases, 10th Revision) at in- or outpatient care during the two years before the index date was required for inclusion in the study.

Monotherapy was defined as no dispensation of any other first- or second-generation antipsychotics in the first 30 days after the index date (Figure 1). Two exceptions from this definition of monotherapy were allowed, as per the dosing recommendations in the *Summary of Product Characteristics* (SmPC) of RLAI[13] and PP3M.[14] These exceptions were temporary supplementation with RISP at the initiation of RLAI and a switch from PP1M to PP3M. For risperidone-treated patients, the patient was classified to the RLAI group if both therapies (RLAI and RISP) fulfilled the classification criteria. In case of paliperidone-treated patients, if PP1M fulfilled the classification criteria first but a PP3M dispensation was present later during the inclusion period, the patient was classified to the PP3M group.

Newly initiated therapy was defined as no dispensation of the same active ingredient and formulation (oral or LAI) for at least six months before the index date.

Outcomes

Baseline patient characteristics of interest included age, gender, and duration since the first diagnosis of schizophrenia. The primary outcome of this study was all-cause 1-year and 1.5-year discontinuation of the newly initiated antipsychotic medication. We evaluated the likelihood of all cause-discontinuation as well as the median time till discontinuation. The method of determining the date of discontinuation was analogous to the methods presented in publications of previous studies on the same database.[12,15]

Patients were considered to have discontinued their antipsychotic medication if it was not dispensed after their estimated end date of exposure plus a grace period of 60 days. The day of the first dispensing of an antipsychotic was considered as the first day of the exposure to

this drug. For every antipsychotic drug, including LAIs—except for PP1M, RLAI, and PP3M—the number of treatment days were calculated as the total amount of the prescribed medication (mg) divided by the defined daily dose.[16] For PP1M, RLAI, and PP3M, dosage according to the specific prescription (based on SmPCs) was used in the calculation. The date of discontinuation was estimated as end of treatment of last dispensation for the given drug as explained above unless another antipsychotic was prescribed earlier or during the grace period. Patients were censored in case of death during the observation period.

Statistical analysis

The statistical analysis was similar to our previous study.[12] Means and standard deviations for continuous variables and counts and percentages for categorical variables were calculated. Kaplan-Meier survival analysis was performed to estimate the median survival times until all-cause discontinuation and the 1- and 1.5-year survival probabilities of the predefined monotherapy groups. Further analysis of LAI wherein Kaplan-Meier survival functions were stratified according to the previous treatment i.e. whether patients had switched from another LAI or from an OAP (or no treatment) in the previous 60 days, were also performed. Since PP3M needs to be initiated with PP1M, this analysis was not performed for PP3M. Comparison of patients on LAIs who switched from oral treatment and those who switched from another LAI enabled us to examine the importance of long-term treatment stability, and to investigate whether prior exposure to LAI treatment may be associated with a better adherence to subsequent LAIs.

Pairwise comparison of treatments was carried out by Cox proportional hazards regression models to evaluate the likelihood of treatment discontinuation. Hazard ratios (HR) and 95% confidence intervals (CI) were determined. In order to increase the comparability of the treatment arms, propensity score-based adjusted Cox models were also fitted, with the propensity score based on the following parameters: gender, age at baseline, previous

comorbidities, number and length of previous hospitalization/s in psychiatric wards, and medication compliance. Supplementary Table S1 shows the variables used in the calculation of the propensity score. Patients were partitioned into five subgroups based on the propensity score quintiles.[17, 18] Two Cox models were used in each comparison, and they differed only in the set of covariates. In the first model ('raw'), the only covariate was the administered treatment, while in the second model ('adjusted'), gender, age, and propensity quantile were also included as covariates. Significance level was assessed with reference to an *a priori* set α level of 0.05. All statistical tests were performed using R software (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

Population characteristics

Among the 5,400 patients included in the study, 3,977 (73.6%) were OAP users and 1,423 (26.4%) were LAI users. The mean (SD) age of the patients ranged from 42.7 (13.5) years (OLAI group) to 55.9 (15.3) years (QUET group). The proportion of younger patients (20–40 years) varied from 19.2% (QUET and RISP groups) to 47.2% (ALAI group). The proportion of males was lower than females in all the groups ranging from 34.8% in the ALAI group to 48.6% in the RLAI group. The mean duration since the first recorded F20 diagnosis ranged from 5.1 to 7.2 years. A minimum of 64% of the patients in every group received the first diagnosis >4 years before inclusion in the study (Table 1).

Outcomes

All-cause discontinuation

We estimated 1-year and 1.5-year discontinuation using Kaplan-Meier survival analysis. The likelihood of treatment continuation for patients receiving LAIs was generally higher than for those receiving OAPs. The 1-year continuation with OAPs ranged from 12.7%

(RISP) to 34.1% (OLAN) while the analogous data for LAI ranged from 26.4% (RLAI) to 78.6% (PP3M). Similarly, the 1.5-year survival continuation rates were between 9.3%–29.5% for OAPs and 24.9%–76.4% for LAIs (Table 2 and Supplementary Figure S1). Supplementary Table S2 and Supplementary Table S3 shows the time to all-cause discontinuation of all agents and estimated median percentile of time to all-cause discontinuation respectively.

We also evaluated median time to treatment discontinuation since initiating the new SGA. RLAI was the only LAI whose median (95% CI) time to discontinuation (125 [64–196]) days was numerically lower than some OAPs such as OLAN (151 [130–172]) days and ARIP (152 [134–168]) days. The median (95% CI) time to discontinuation varied in the oral group from 52 (33–67) days (CLOZ) to 152 (134–168) days (ARIP). The median (95% CI) time to discontinuation of LAIs ranged from 125 (64–196) days (RLAI) to 491 (250–not reached) days (ALAI). The discontinuation rate did not reach 50% during the observation period for patients on PP3M (Table 3).

Pairwise comparisons for the risk of all-cause discontinuation

As this study focused on the treatment discontinuation of LAIs, each LAI was compared with all the other treatments using unadjusted ('raw') and adjusted pairwise Cox proportional hazards regression analyses (Table 4). Based on the unadjusted analyses, the risk of all-cause discontinuation was significantly higher for all the OAPs when compared with PP1M, OLAI, PP3M, and ALAI (P<0.01 for all). Compared to RLAI, the risk of treatment discontinuation was significantly higher only for CLOZ (HR = 1.47, 95% CI 1.11–1.94) and RISP (HR = 1.62, 95% CI 1.23–2.14) (P<0.01 for all). In the adjusted analysis, the risk of all-cause discontinuation was significantly higher in all the OAPs when compared with PP3M and ALAI (P<0.01 for all). Compared to PP1M, the risk of discontinuation was significantly higher for all the OAPs except OLAN and PALI. Similarly, the risk of discontinuation was

not significantly different between OLAI and PALI. The risk of discontinuation with RLAI was significantly lower than with RISP (P<0.001; Table 4).

Based on unadjusted analyses, all LAIs had a significantly higher risk of discontinuation than PP3M (P<0.001). ALAI had a significantly lower risk of discontinuation than PP1M and RLAI (P<0.05 for all), while PP1M and OLAI had a significantly lower risk of discontinuation than RLAI (P<0.01 for all). In the adjusted analysis, all LAIs had a significantly higher risk of discontinuation than PP3M (P<0.05), while ALAI had a significantly lower risk of discontinuation than all the LAIs except PP3M (P<0.05 for all). PP1M had a significantly lower risk of discontinuation than RLAI (P<0.001; Table 4).

Impact of prior treatment on treatment discontinuation with LAIs

Patients who switched from a prior LAI treatment to PP1M achieved a significantly longer time on treatment than patients who either switched from oral treatment or from no previous treatment. Among these patients, the proportion of patients who discontinued treatment during the study was <50%, hence, the median time could not be calculated during the follow-up period (Table 5). Rates of 1-year continuation in the various PP1M subgroups were 35.0% in the non-previous LAI treated group, 39.8% in the total group, and 56.8% in the previous LAI treated group, while 1.5-year continuation rates were 31.4%, 35.9%, and 51.6%, respectively (Figure 2).

RLAI users who switched from a prior LAI treatment achieved longer time on treatment than patients who switched from oral or no previous treatment. On the other hand, OLAI users who switched from oral treatment or no previous treatment achieved longer time on treatment than patients who switched from prior LAI treatment. However, since the sample size of patients in the RLAI and OLAI groups who had prior LAI treatment was small, these results cannot be considered as robust estimates (Table 5). The median time to discontinuation in patients without prior LAI treatment was 121 days and 301 days for those

on RLAI and OLAI, respectively. The estimate for patients on OLAI who switched from another LAI was 61 days. Among patients who switched from another LAI to RLAI, the proportion of patients who discontinued treatment during the study was <50%, hence, the median time could not be calculated during the follow-up period (Table 5).

Discussion

The current study is an update of a previous analysis[12] wherein claims data of Hungarian patients with schizophrenia were assessed till 2015. However, as new LAIs such as ALAI and PP3M were launched in Hungary since the previous analysis, we included the new LAIs in the current analysis on antipsychotic treatment discontinuation after usage for 1 and 1.5 years. Overall, in the current study, patients on LAIs were more likely to continue their treatment after 1 and 1.5 years than patients on OAPs, although in the RLAI vs AMIS, RLAI vs OLAN, RLAI vs PALI, RLAI vs QUET comparisons LAI treatment arms did not show statistical significance.

The 1-year continuation rate in the current study (12.7%–34.1% for OAPs and 26.4%–78.6% for LAIs) was similar to our previous analysis (17%–31% for OAPs and 32%–64% for LAIs),[12] although introduction of ALAI and PP3M in the current study increased the upper limit of the 1-year continuation rate. The median time to discontinuation in both studies was greater for LAIs than for OAPs. In pairwise comparisons to assess the likelihood of treatment discontinuation, we observed that OAPs have a higher risk of treatment discontinuation compared with LAIs in both studies. However, individual pairwise comparisons showed some differences. For instance, the adjusted risk of treatment discontinuation with PP1M was significantly lower compared with all OAPs in the previous study, but not in the current study. These differences could have occurred since patients in the previous study did not have the option of discontinuing PP1M and initiating another treatment, whereas patients in the current study had the option of initiating PP3M; as well as

due to the varying patient inclusion periods. PPM3 discontinuation rate was observed to be lower as compared to all other LAIs in this study. LAIs with less frequent dosing may be more convenient for patients for various reasons, e.g. having less frequent pain associated with the injections; for those having difficulty remembering taking their medication or facing issues with transportation or access to healthcare services. Also, fewer injections are associated with less social stigma as reported in various real-world studies.[7-12]

The results of the current study are consistent with previous reports from multiple countries and health systems. Bitter et al[15] analyzed NHIF data from 2006 to 2008 and reported a greater median time to discontinuation as well as lower risk of treatment discontinuation with RLAI. Greene et al [7] analyzed Medicaid data and reported that the discontinuation rate was lower among patients on LAIs than OAPs (63.2% vs. 72.0%; P<0.001). Another study using Medicaid data reported patients on SGA LAIs to be more adherent than those on OAPs to their prescribed index medication after a year of follow-up (27.2% vs. 24.6%; P<0.05).[19] Previous researchers have also reported the greater risk of antipsychotic treatment discontinuation among patients on OAPs. Greene et al [7] reported a 20% greater risk of antipsychotic discontinuation among OAP users (HR = 1.20, 95% CI 1.13–1.28; P<0.001) while Verdoux et al[20] compared propensity score-matched French patients with schizophrenia who were initiated on LAIs or OAPs and reported greater treatment discontinuation among OAP users (69%) vs. LAI users (57%) (adjusted relative risk = 1.6, 95% CI 1.23–2.07).

Similar to our previous study,[12] we observed a difference in time to discontinuation between the PP1M-treated group where patients were switched from one LAI to another and the group where patients were switched to an LAI from oral or no treatment. The time to discontinuation was longer in patients on PP1M who switched from previous LAI treatment compared to oral/no treatment to LAI switchers. Although differences were also observed in

patients treated with RLAI and OLAI, the results are not reliable since only a few patients had prior LAI treatment in these groups. The better outcome observed among LAI-LAI switchers could be attributed to the patients' preference for their current drug formulation, as patients have reported that they would prefer continuing with their current formulation.[21] We could not complete the evaluation of this outcome among patients on PP3M since PP1M needs to be used prior to PPM3.

Previous European studies have associated LAI usage with fewer relapses, symptomatic improvement, increased personal recovery, lower suicidal ideation and fewer suicide attempts.[22-24] as well as lower risk of hospitalization and treatment costs.[25, 26] Corigliano et al[24] and Brown et al[27] have reported that patients in the early stages of schizophrenia seemed to benefit more from LAI initiation than chronic patients. Early LAI initiation was also associated with fewer hospitalizations and lower costs in the US.[28] Although LAIs have been associated with significant benefits, they are often prescribed only to non-adherent patients, and patients with first-episode schizophrenia are hardly considered suitable candidates.[29] Clinician-related barriers such as beliefs about LAIs being associated with greater adverse events, lack of knowledge and resources; as well as patient-related barriers such as fear of injection, injection site pain, stigma, and cost, negatively impact the uptake of LAIs in clinical practice.[30] However, as increasing evidence supporting the benefits of LAIs become available, approaches to train clinicians and their staff as well as educate patients are required.

Limitations

There are a few limitations of the present study. An inherent disadvantage of real-world studies is the lack of randomization, leading to potential lack of comparability between different patient groups. However, we addressed this issue by performing both raw and adjusted pairwise analyses while comparing individual treatments. Due to the inherent nature

of health claims data, it is possible that a diagnosis of schizophrenia was a result of misclassification or coding errors. Claims data also insufficiently reflect disease severity and other influencing circumstances. Claims data may have selection bias of different treatments, e.g. newly diagnosed patients must be treated with OAPs first and only then switched to LAIs. However, as this rule is applied only to the first episode of schizophrenia, this bias is not likely to be considerable. The exact start and end dates of treatment could not be specified, hence, we had to estimate the dates for these cases. The algorithm used to determine continuous treatment may allow patients to have gaps in treatment with considerable length, which may cause that some of the patients have a lower medication possession ratio due this reason (i.e., patients being off medication for periods or taking lower dose than DDD). This can have different effects for orals and LAIs, and they were not formally addressed in the study. This study used treatment discontinuation as the outcome. There are other events that may signal the inefficiency of therapy, such as starting another antipsychotic as polytherapy; these were not assessed in the current study. Drug usage data during hospitalization could not be obtained from the database. Patients being admitted to a psychiatric ward can indicate ineffectiveness of therapy, but these were not assessed directly. We assumed that in the vast majority of the cases patients who were hospitalized in a psychiatric ward would get a different treatment after being discharged from the hospital which would count as a treatment discontinuation. Use of other psychiatric medications, such as mood stabilizers, antidepressants, benzodiazepines or benzodiazepine-related drugs might indicate the ineffectiveness of antipsychotics as well, however, these were not controlled for in the study. The way patients were assigned to the PP3M group in the study might cause bias in the PP1M group. In the real world, patients are transferred from PP1M to PP3M not at random, but according to the decision of the treating physician. This may result in patients remaining on PP1M to have a tendency towards shorter time to discontinuation, if doctors are

less willing to transfer such patients to PP3M. Also, there were restrictions on data export due to privacy reasons. The actual number of patients could not be reported in groups where the number of patients was <10.

Conclusion

This study provides evidence from a full populational study regarding the advantage of LAIs compared with OAPs in terms of time to treatment discontinuation. Our results also suggest that better clinical stability could be achieved by switching from one LAI to another, if required. Future research could evaluate long-term effect of LAIs on parameters such as death, hospitalization, co-medication, or suicide.

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Figure Legends

Figure 1. Study design

*****At the observation start (index date): No dispensation of different antipsychotic in the following 30 days. No dispensation of the same treatment in the 6 months preceding. At least 1 instance of F20 diagnosis in the 2 years preceding.

Figure 2. Kaplan-Meier survival of PP1M treated subgroups with 60 days grace period

Abbreviation: LAI – Long Acting Injectable, PP1M - paliperidone long-acting injection 1 monthly

Table 1: Baseline characteristics

	AMIS	ARIP	CLOZ	OLAN	QUET	PALI	RISP	ALAI	OLAI	PP1M	PP3M	RLAI
Total population (n)	255	679	561	862	893	163	692	89	108	364	627	72
Male, n (%)	103 (40)	265 (39)	258 (46)	402 (47)	321 (36)	71 (44)	284 (41)	31 (35)	51 (47)	164 (45)	295 (47)	35 (49)
Age at baseline (years)												
Mean	51.65	46.32	51.84	48.62	55.90	46.69	54.02	43.24	42.73	48.76	48.64	51.83
SD	14.99	14.39	15.24	15.32	17.31	13.68	17.56	13.07	13.50	13.96	12.76	14.95
Median	52	45	53	48	57	47	55	41	41.5	50	48	53
25^{th}-75^{th} percentile	40.5 – 62	36 – 57.5	39 – 63	37 – 60	43 – 68	36 – 57	41 – 67	34 – 53	31 – 53.25	38 – 60	38 – 59	40.8 – 63.2
Population by age groups, n (%)												
20 – 29	15 (6)	91 (13)	36 (6)	96 (11)	58 (6)	17 (10)	54 (8)	11 (12)	21 (19)	35 (10)	40 (6)	-
30 – 39	41 (16)	147 (22)	101 (18)	161 (19)	113 (13)	33 (20)	79 (11)	31 (35)	22 (20)	76 (21)	137 (22)	13 (18)
40 – 49	53 (21)	155 (23)	104 (19)	187 (22)	154 (17)	44 (27)	143 (21)	20 (22)	27 (25)	67 (18)	154 (25)	15 (21)
50 – 59	59 (23)	138 (20)	122 (22)	181 (21)	182 (20)	32 (20)	122 (18)	13 (15)	21 (19)	94 (26)	151 (24)	16 (22)
60 – 69	56 (22)	99 (15)	117 (21)	146 (17)	184 (21)	29 (18)	139 (20)	12 (13)	14 (13)	69 (19)	114 (18)	13 (18)
70 –	28 (11)	42 (6)	76 (14)	82 (10)	198 (22)	-	142 (21)	-	-	23 (6)	31 (5)	11 (15)
Time since diagnosis[a]												
Mean	72.29	72.09	81.59	70.90	61.61	77.80	66.26	67.51	64.47	74.86	80.02	66.83
SD	34.39	32.31	26.93	33.09	37.28	29.79	35.91	35.92	34.74	32.10	26.10	36.87
< 6 months[b], n (%)	17 (7)	33 (5)	12 (2)	55 (6)	120 (13)	-	70 (10)	-	-	20 (5)	-	-
6 – 48 months[c], n (%)	50 (19)	139 (20)	64 (11)	170 (20)	199 (22)	27* (17)	144 (21)	27* (30)	33* (31)	60 (16)	91* (15)	23* (32)
> 48	188 (74)	507 (75)	485 (86)	637 (74)	574 (64)	136 (83)	478 (69)	62 (70)	75 (69)	284 (78)	536 (85)	49 (68)

months[d], n (%)												

Some parameters are left blank as the data holder (NHIF) does not make data available for groups with <10 patients.
[a] time since first diagnosis appearance in the database does not necessarily mean the first diagnosis ever, as the date of the first diagnosis is not recorded. Data before 2002 were not available
[b] time since first diagnosis occurred in the database was within 6 months before inclusion.
[c] time since first diagnosis occurred in the database was > 6 months but < 48 months before inclusion.
[d] time since first diagnosis occurred in the database was > 48 months before inclusion.
*The two groups (6 – 48 months and > 48 months) could not be split due to low patient count in one of the groups.
Abbreviations: ALAI – aripiprazole long-acting injection, AMIS – oral amisulpride, ARIP – oral aripiprazole, CLOZ – oral clozapine, NHIF – National Health Insurance Fund, OLAI – olanzapine long-acting injection, OLAN – oral olanzapine, PALI – oral paliperidone, PP1M – paliperidone long-acting injection 1 monthly, PP3M – paliperidone long-acting injection 3 monthly, QUET – oral quetiapine, RISP – oral risperidone, RLAI – risperidone long-acting injection, SD – Standard Deviation

Table 2: Proportion of patients continuing newly initiated antipsychotic during the follow-up period

Treatment	PP3M	ALAI	OLAI	PP1M	RLAI	OLAN	PALI	ARIP	QUET	CLOZ	RISP
Observation time elapsed (days)[a]	n=627	n=89	n=108	n=364	n=72	n=862	n=163	n=679	n=893	n=561	n=692
181	0.90	0.67	0.57	0.57	0.39	0.45	0.44	0.43	0.34	0.28	0.21
361	0.79	0.56	0.46	0.40	0.26	0.34	0.31	0.29	0.23	0.16	0.13
541	0.76	0.49	0.43	0.36	0.25	0.30	0.27	0.23	0.19	0.13	0.09

[a]Time elapsed from the initiation of new treatment during the follow-up period.
Estimates for the proportion of the patients on the initially assigned medication at each time point are based on the non-parametric Kaplan Meier approach.
Abbreviations: ALAI – aripiprazole long-acting injection, ARIP – oral aripiprazole, CLOZ – oral clozapine, OLAI – olanzapine long-acting injection, OLAN – oral olanzapine, PALI – oral paliperidone, PP1M – paliperidone long-acting injection 1 monthly, PP3M – paliperidone long-acting injection 3 monthly, QUET – oral quetiapine, RISP – oral risperidone, RLAI – risperidone long-acting injection

Table 3: Median time in days elapsed to all-cause discontinuation since the start of treatment

Group	Lower 25th percentile	Median	Upper 25th percentile
CLOZ	33	**52**	67
RISP	48	**56**	66
QUET	68	**80**	90
AMIS	75	**90**	110
PALI	89	**116**	211
RLAI	64	**125**	196
OLAN	130	**151**	172
ARIP	134	**152**	168
PP1M	202	**236**	303
OLAI	168	**289**	not reached
ALAI	250	**491**	not reached
PP3M	not reached	**not reached**[a]	not reached

[a]More than 50% of patients stayed on the treatment within the observation period (1.5 years).
Median time to all-cause discontinuation is based on the non-parametric Kaplan Meier approach.
Abbreviations: ALAI – aripiprazole long-acting injection, AMIS – oral amisulpride, ARIP – oral aripiprazole, CLOZ – oral clozapine, OLAI – olanzapine long-acting injection, OLAN – oral olanzapine, PALI – oral paliperidone, PP1M – paliperidone long-acting injection 1 monthly, PP3M – paliperidone long-acting injection 3 monthly, QUET – oral quetiapine, RISP – oral risperidone, RLAI – risperidone long-acting injection

Table 4: Raw (unadjusted) and propensity-score adjusted pairwise comparisons of LAIs and OAPs for all-cause discontinuation

	PP1M	RLAI	OLAI	PP3M	ALAI	AMIS	ARIP	CLOZ	OLAN	PALI	QUET	RISP
Raw HR and 95% CI[a]												
PP1M	-	**1.58**	**0.86**	**0.24**	**0.67**	**2.01**	**1.35**	**2.25**	**1.27**	**1.39**	**1.81**	**2.54**
		(1.176-2.128)	(0.649-1.14)	(0.197-0.299)	(0.486-0.932)	(1.665-2.425)	(1.151-1.573)	(1.92-2.634)	(1.088-1.474)	(1.108-1.733)	(1.557-2.096)	(2.177-2.956)
		p=0.002	p=0.294	p<0.001	p=0.017	p<0.001	p<0.001	p<0.001	p=0.002	p=0.004	p<0.001	p<0.001
RLAI	**0.63**	-	**0.57**	**0.15**	**0.44**	**1.25**	**0.85**	**1.47**	**0.81**	**0.88**	**1.2**	**1.62**
	(0.47-0.85)		(0.394-0.822)	(0.108-0.203)	(0.297-0.664)	(0.927-1.687)	(0.642-1.126)	(1.107-1.944)	(0.617-1.076)	(0.634-1.211)	(0.908-1.579)	(1.227-2.143)
	p=0.002		p=0.003	p<0.001	p<0.001	p=0.143	p=0.257	p=0.008	p=0.149	p=0.423	p=0.202	p<0.001
OLAI	**1.16**	**1.76**	-	**0.28**	**0.79**	**2.22**	**1.55**	**2.56**	**1.44**	**1.56**	**2.04**	**2.83**
	(0.877-1.542)	(1.217-2.537)		(0.205-0.374)	(0.535-1.169)	(1.67-2.965)	(1.186-2.02)	(1.961-3.348)	(1.109-1.88)	(1.146-2.134)	(1.569-2.65)	(2.175-3.693)
	p=0.294	p=0.003		p<0.001	p=0.239	p<0.001	p=0.001	p<0.001	p=0.006	p=0.005	p<0.001	p<0.001
PP3M	**4.11**	**6.76**	**3.61**	-	**2.79**	**8.59**	**5.61**	**8.72**	**4.92**	**5.83**	**6.78**	**9.97**
	(3.341-5.064)	(4.932-9.265)	(2.676-4.87)		(1.987-3.925)	(6.915-10.665)	(4.66-6.757)	(7.217-10.536)	(4.105-5.908)	(4.559-7.467)	(5.664-8.12)	(8.281-11.997)
	p<0.001	p<0.001	p<0.001		p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
ALAI	**1.49**	**2.25**	**1.26**	**0.36**	-	**2.87**	**2**	**3.14**	**1.83**	**1.99**	**2.56**	**3.57**
	(1.073-2.057)	(1.505-3.369)	(0.856-1.869)	(0.255-0.503)		(2.061-3.997)	(1.467-2.739)	(2.298-4.303)	(1.345-2.499)	(1.404-2.835)	(1.879-3.481)	(2.617-4.876)
	p=0.017	p<0.001	p=0.239	p<0.001		p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Adjusted HR and 95% CI[b]												
PP1M	-	**1.73**	**0.77**	**0.26**	**0.62**	**1.6**	**1.33**	**1.45**	**1.17**	**1.14**	**1.45**	**2.16**
		(1.253-2.376)	(0.533-1.125)	(0.13-0.517)	(0.419-0.907)	(1.23-2.079)	(1.091-1.622)	(1.158-1.816)	(0.969-1.405)	(0.878-1.479)	(1.2-1.753)	(1.801-2.596)
		p<0.001	p=0.179	p<0.001	p=0.014	p<0.001	p=0.005	p=0.001	p=0.104	p=0.327	p<0.001	p<0.001
RLAI	**0.58**	-	**0.68**	**0.19**	**0.47**	**1.24**	**1.06**	**1.28**	**0.86**	**0.9**	**1.28**	**1.67**
	(0.421-0.798)		(0.382-1.219)	(0.113-0.304)	(0.252-0.882)	(0.814-1.894)	(0.759-1.469)	(0.881-1.873)	(0.63-1.171)	(0.591-1.38)	(0.935-1.745)	(1.237-2.244)
	p<0.001		p=0.197	p<0.001	p=0.019	p=0.315	p=0.747	p=0.194	p=0.336	p=0.637	p=0.125	p<0.001
OLAI	**1.29**	**1.46**	-	**0.37**	**0.48**	**1.78**	**1.48**	**1.61**	**1.38**	**1.27**	**1.54**	**2.52**
	(0.889-1.875)	(0.82-2.615)		(0.193-0.704)	(0.237-0.976)	(1.161-2.739)	(1.088-2.002)	(1.151-2.246)	(1.023-1.857)	(0.742-2.162)	(1.146-2.078)	(1.853-3.437)
	p=0.179	p=0.197		p=0.002	p=0.043	p=0.008	p=0.012	p=0.005	p=0.035	p=0.386	p=0.004	p<0.001
PP3M	**3.85**	**5.39**	**2.71**	-	**1.85**	**6.7**	**4.34**	**5.29**	**3.76**	**6.15**	**4.04**	**6.4**
	(1.933-7.672)	(3.288-8.838)	(1.421-5.182)		(1.098-3.125)	(4.087-10.98)	(3.119-6.049)	(3.613-7.755)	(2.284-6.191)	(3.365-11.242)	(2.436-6.708)	(4.398-9.314)
	p<0.001	p<0.001	p=0.002		p=0.021	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
ALAI	**1.62**	**2.12**	**2.08**	**0.54**	-	**2.75**	**1.99**	**2.34**	**1.82**	**1.96**	**2.23**	**3.63**
	(1.103-2.387)	(1.133-3.976)	(1.024-4.212)	(0.32-0.911)		(1.722-4.403)	(1.425-2.791)	(1.58-3.465)	(1.296-2.552)	(1.247-3.082)	(1.583-3.129)	(2.539-5.186)
	p=0.014	p=0.019	p=0.043	p=0.021		p<0.001	p<0.001	p<0.001	p<0.001	p=0.004	p<0.001	p<0.001

[a] higher value means higher probability of staying on treatment in the first column

[b] propensity score adjustments

Abbreviations: ALAI – aripiprazole long-acting injection, AMIS – oral amisulpride, ARIP – oral aripiprazole, CI – confidence interval, CLOZ – oral clozapine, HR – hazard ratio, LAIs – long-acting injectables, OAPs – oral antipsychotics, OLAI – olanzapine long-acting injection, OLAN – oral olanzapine, PALI – oral paliperidone, PP1M – paliperidone long-acting injection 1 monthly, PP3M – paliperidone long-acting injection 3 monthly, QUET – oral quetiapine, RISP – oral risperidone, RLAI – risperidone long-acting injection

Table 5: Estimates of median time and lower and upper quartiles of days elapsed to treatment discontinuation in different treatment groups as a function of prior treatment

Treatment arm	Patient group	25th percentile	Median	75th percentile
RLAI (n>62)	no Previous LAI [a]	31	**121**	301
OLAI (n>98)	no Previous LAI	91	**301**	not reached
PP1M (n=283)	no Previous LAI	61	**211**	not reached
RLAI (n=72)	Total [b]	31	**151**	391
OLAI (n=108)	Total	91	**301**	not reached
PP1M (n=364)	Total	91	**241**	not reached
RLAI (n<10)	Previous LAI [c] treatment	91	**not reached**	not reached
OLAI (n<10)	Previous LAI treatment	61	**61**	not reached
PP1M (n=81)	Previous LAI treatment	211	**not reached**	not reached

[a] No previous LAI means the patient were not treated within 60 days with any other available LAI treatment before starting to the respective arm
[b] Total means all patients were considered in the respective arm, independently from their previous treatment
[c] Previous LAI treatment means the patient was treated within 60 days with any other available LAI treatment before starting to the respective arm.
Abbreviations: LAI – long-acting injection, OLAI – olanzapine long-acting injection, PP1M - paliperidone long-acting injection 1 monthly, RLAI – risperidone long-acting injection

Figure 1

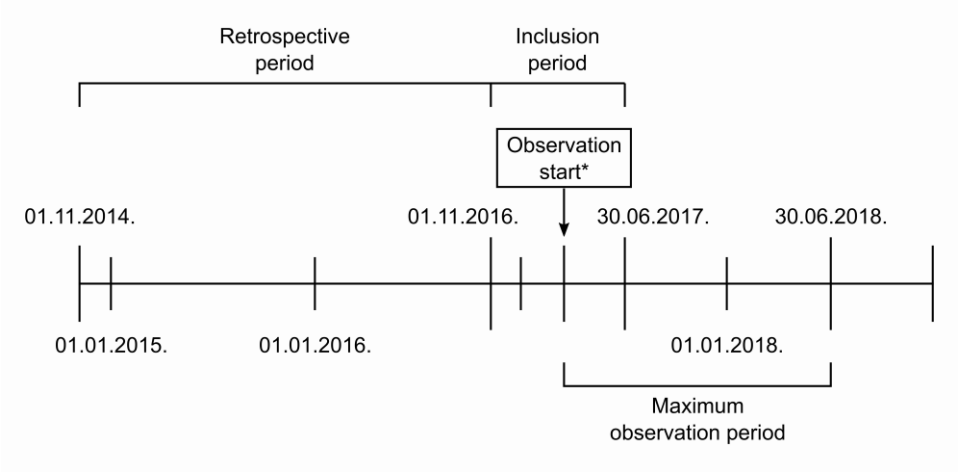

Figure 2