Second-generation LAI are associated to favorable outcome in a cohort of incident patients diagnosed with schizophrenia

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Title: Second-generation LAI are associated to favorable outcome in a cohort of incident patients diagnosed with schizophrenia

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Abstract

Objective

Investigate the associations of long-acting injectable (LAI) second generation antipsychotic drugs with number of relapses, psychiatric admissions, days hospitalized, intentional self-harm events, and costs linked to hospitalizations in incident patients diagnosed with schizophrenia.

Method

A nationwide, population-based, retrospective study utilizing mirror-image models before and after initiation of LAI SGA.

Results

10,509 patients were included as study population, with analyses being conducted on 2,223 patients in a six-month period, 1,383 in a 12-month period, 713 in a 24-month period. After initiation of LAI antipsychotics, patients experienced a reduction in number of relapses with an incidence rate ratio (IRR) of 0.60 for the first six months, IRR 0.64 for the first 12 months and IRR 0.64 for the first 24 months following initiation of LAI, all P<0.001. The number of psychiatric admissions was reduced in a similar manner with respective IRR of 0.59, 0.60 and 0.64, all P<0.001. Psychiatric bed-days were reduced with 58, 100 and 164 days for the respective periods after LAI initiation, all P<0.001. In a Cox regression model in patients initiated on LAI, higher age at diagnosis, hazard rate ratio (HR) 0.99, 95%CI(0.98–0.99), P<0.001, and a later calendar year of diagnosis, HR 0.99, 95%CI(0.98-1.00), P<0.05, were associated with a lower risk of relapse, whereas mainly psychiatric comorbidity, HR 1.07, 95% CI (1.04-1.11), P<0.001, and cardiovascular disease, HR 1.12, 95%CI(1.01-1.26), P<0.05, were associated with relapse.

Conclusion

Even though the design does not allow inferences regarding causality, these population-based findings support the use of second generation LAI antipsychotics.

Keywords:

Schizophrenia

Antipsychotic

Long-acting injectables

Relapse

Pharmacoepidemiology

1. Introduction

In patients newly diagnosed with schizophrenia different trajectories of clinical course in terms of psychopathology, hospitalizations and response to treatment have been demonstrated to be associated with duration of untreated psychosis, age at onset, previous hospitalizations, socioeconomic status and social and general function (Austin et al., 2015; Jäger et al., 2014; Levine and Rabinowitz, 2010). In general, patients newly diagnosed with schizophrenia respond well to antipsychotic drugs (Kahn et al., 2008), but based on the randomized clinical trials (RCTs) conducted in this population it has not been possible to elucidate a hierarchy of antipsychotic drugs regarding their effect (Zhu et al., 2017). Thus, the newest network meta-analysis mainly guides treatment choices on side-effect profiles of the different available antipsychotic drugs and suggests for that reason to avoid haloperidol (Zhu et al., 2017). Despite of drug induced initial symptom reduction, and even remission in some patients with newly diagnosed schizophrenia, discontinuation rates are high, resulting in relapse and hospitalization (Kahn et al., 2008; Whale et al., 2016). It is still uncertain how to manage patients with newly diagnosed schizophrenia who do not respond to the initial treatment, but the currently ongoing OPTIMISE study, evaluating a stepped pharmacological treatment program with aggressive treatment for non-responders is expected to result in more clear guidelines for clinicians (Leucht et al., 2015). Early intervention studies in patients newly diagnosed with schizophrenia have in general shown a positive effect on symptoms, social function and risk of admission while patients were enrolled but effects have diminished over time when patients returned to standardized treatment (Albert et al., 2017; Chan et al., 2015; Norman et al., 2011). The lack of a sustained effect of these interventions, which in many cases is the result of a discontinuation of a successful or partially successful treatment with an oral antipsychotic has resulted in LAI antipsychotics being proposed as an early treatment option, to increase adherence to treatment and thereby hopefully to decrease the risk of relapse, hospitalization and deterioration of social function and quality of life (Correll et al., 2016; Stahl, 2014). With the emergence of several second generation antipsychotic drugs as LAI, the treatment armamentarium has not only expanded but also improved, because the side effect profiles of the second generation antipsychotic LAI are more favorable

than those of the first generation antipsychotic LAI (Correll et al., 2016). Also, the different side effect profiles within the group of second generation antipsychotic LAI provide clinicians with the possibility of letting treatment choice be guided by side-effects profiles combined with individual patient tolerability (Correll et al., 2016).

In the current study, we wished to investigate if a change from oral antipsychotic treatment to LAI second generation antipsychotic drugs was associated with changes in number of relapses, number of admissions, use of bed days, occurrence of intentional self-harm and treatment cost, utilizing a mirror-image design in a nationwide population. We also wished to identify explanatory variables associated with relapse in patients treated with LAI second generation antipsychotics utilizing a Cox regression model.

2. Materials and methods

2.1. Registers used

Data on psychiatric contacts and psychiatric disorders were retrieved from the Danish Psychiatric Central Research Register (DPCRR) (Mors et al., 2011). Data on hospital contacts and somatic diseases were retrieved from the Danish National Patient Register (NPR)(Lynge et al., 2011). Data on prescription of medication were retrieved from the Danish National Prescription Registry (DNPR) with data available from 1995 and onwards (Gaist et al., 1997).

All register data are linked to each individual patient via the unique personal identification number (CPR) assigned to all residents at birth or upon immigration (Munk-Jorgensen and Ostergaard, 2011).

Data are not accessable to the public, and access is only provided upon approval from The Danish Data Protection Agency and the Danish Health Authority and Statistics Denmark.

2.2 . Design

A nationwide, population-based, retrospective study.

2.3. Population

Patients diagnosed with schizophrenia (ICD-10 F20.x) for the first time between January 1st 1996 and December 31st 2013, who had been prescribed a LAI second generation antipsychotic (Anatomical Therapeutic Chemical Classification System (ATC) codes N05AX12 (aripiprazole), N05AH03 (olanzapine), N05AX13 (paliperidone) or N05AX08 (risperidone), i.e. second generation antipsychotic LAI available in Denmark in the study period) were identified. Patients diagnosed with schizophrenia (ICD-8 300 or ICD-10 F20.x) before January 1st 1996 were excluded, as well as patients treated with second generation antipsychotic LAI before the schizophrenia diagnosis was registered. Thereby constructing a cohort of incident patients diagnosed with schizophrenia followed until initial treatment with a second generation antipsychotic LAI.

From 2008 onwards all incident patients diagnosed with schizophrenia had antipsychotic drugs dispensed free of charge through hospital pharmacies during the first two years of treatment implying that no prescriptions were registered during these two years. To ascertain if patients were exposed to the shortest mirror image period (six months) a lag time of two years plus half a year of mirror image period was needed, resulting in all patients from January 1st 2008 until December 31st 2013 being included with 913 days of delay from diagnosis.

2.4. Outcome measures

2.4.1. Number of relapses

Relapse was defined as either hospitalisation in a psychiatric ward or hospital contact in a somatic/psychiatric ward due to intentional self-harm (ICD-10 X64-X80). Number of relapses were the sum of occurrences of these events.

2.4.2. Number of psychiatric hospital admissions

Defined as number of admissions to a psychiatric ward regardless of diagnosis.

2.4.3. Number of psychiatric in-hospital bed days

Defined as number of bed days in connection with a hospitalisation in a psychiatric ward in patients admitted.

2.4.4. Intentional self-harm

Defined as number of hospital contacts to a somatic/psychiatric ward due to intentional self-harm (ICD-10 X64-X80).

2.4.5. Hospital costs

Defined as the sum of Danish standard hospitalisation tariffs for all hospital contacts for all admissions per day hospitalized and for all outpatient contacts for each defined mirror image period (Sundhedsdatastyrelsen, n.d.).

2.5. Statistical analysis

The primary analysis was a mirror-image analysis of number of events defined under outcome measures in mirror image periods of 6, 12, and 24 months. The index of the mirror was defined as initiation of LAI. The retrospective and prospective window was defined as of equal length in each participant, and consisted of periods of 6, 12, and 24 months retrospectively and prospectively. Patients were included in all periods for which they could deliver full observation time on treatment, e.g. a patient could be included in several mirror windows, but only if they continued LAI throughout each of the observation periods.

We employed linear regression for the outcomes; psychiatric in-hospital bed-days and hospital costs, while we used Poisson regression for relapse, psychiatric hospital admissions and intentional self-harm to calculate differences between mirror-image periods. Patients who died, ended LAI treatment or immigrated before the end of study were excluded at that time point.

In addition, we calculated mean values, including confidence intervals, of all outcomes before and after index, respectively.

Sensitivity analyses on effects of missing data on medication during hospitalisations were defined a priori comparing admitted to non-admitted patients, as well as imputing data during hospitalisation from data on LAI antipsychotic drug use before and after hospitalisation.

Furthermore, sensitivity analyses comparing patients diagnosed before and during the freely dispensed antipsychotic drugs were also conducted as defined a priori.

Secondly, we defined a Cox regression model with relapse defined as event, and entry defined as initiation of LAI. The model included severity of primary psychiatric disorder, psychiatric co-morbidity (see below), somatic co-morbidity (see below), as well as age, gender, and year of diagnosis as defined below. Patients were followed until event, end of LAI treatment, death or end of study (whichever came first).

We defined a post-hoc Cox regression model including the same explanatory variables, except for the psychiatric co-morbidity score, which instead was added with each component of co-morbidity (see below) as explanatory variables, as a sensitivity analysis, to evaluate the effects of each psychiatric co-morbidity.

P-values < 0.05 were considered statistically significant.

Statistical analyses were performed with STATA 13 at the Statistics Denmark server with remote access (College Station, 2009).

2.6. Explanatory variables for the Cox regression analysis

2.6.1. Severity of primary psychiatric disorder

The current Danish registers do not include data on severity. Therefore, we used the following variables as proxy markers of disease severity: number of psychiatric admissions, number of psychiatric bed days and number of psychiatric outpatient contacts after incident diagnosis but before LAI initiation for all variables.

2.7. Psychiatric co-morbid disorder

We defined a psychiatric co-morbidity score by a diagnosis in one or more of the following groups: psychosis (ICD-10 F2x.x), affective disorders (ICD-10 ICD 3x.x), substance misuse (ICD-10 F1x.x), other psychiatric diagnosis (remaining ICD-10 Fx.x diagnosis), and intentional self-harm (ICD-10 X64.x to F80.x), with each group resulting in a single point increase on a sum score.

2.8. Somatic co-morbidity

Known somatic disease is a risk factor for additional somatic disease and subsequent hospitalisations, why the presence of cardiovascular diseases (ICD-10 I05.x-I15.x, I20.x-I28.x, I30.x-I52.x, I60.x-I89.x, I95.x-I99.x), diabetes (ICD-10 E10 – E14), chronic obstructive pulmonary disease (ICD-10 J44.x) and hepatitis (ICD-10 B15.x – B19.x), were included as explanatory variables.

3. Results

In the current study we included 10,509 patients (6,358 males and 4,151 females) followed for 5,931 person-years (males 3,869 person-years and females 2,062 person-years), with further demographics described in table 1. Considering the whole study period, not adjusting for duration of follow-up, participants had a mean

of 3.03, 95% CI (2.91 – 3.15) psychiatric admissions before initiation of a second generation antipsychotic LAI (SGA LAI), and a mean of 1.04, 95%CI (0.95 – 1.13) admissions after initiation of SGA LAI. Likewise, before initiation of SGA LAI participants had a mean of 183.74, 95% CI (177.35 – 190.14) psychiatric bed days as compared to 25.36, 95%CI (23.56 – 27.17) after initiation of SGA LAI. Mean hospital costs before initiation of SGA LAI were 432.16, 95% CI (414.40 – 449.91) thousand Danish kroner per patients, as compared to 76.74, 95% CI (71.38 – 82.11) thousand Danish kroner per patient after initiation of SGA LAI. Adjusting for duration of follow-up, the mirror-image analysis with pre- and post-LAI study periods of 6, 12 and 24 months showed a reduction of 35-40 percent in number of relapses for all mirror-image periods after SGA LAI initiation, a reduction of 35-40 percent in number of psychiatric admission for all mirror-image periods after SGA LAI initiation, a reduction of 85 percent in number of days hospitalized in all mirror-image periods after SGA LAI initiation, and a reduction of 75-80 percent in hospital costs, as shown in table 2. We furthermore conducted frequency analyses of number of relapses, psychiatric admissions and psychiatric bed days showing a left shift in frequencies, more patients with a lower number of the specified outcome, after initiation of LAI as compared to before, as shown in figure 1. The results from the mirror-image sensitivity analyses described in the Materials and Methods section showed similar results (data not shown).

Secondly, the analysis of variables associated with relapse risk in patients after initiation of LAI showed that especially psychiatric co-morbidity (Hazard rate ratio (HR) 1.07, 95%CI (1.04 – 1.11), $P < 0.001$) and a diagnosis of cardiovascular disease (HR 1.12, 95% CI (1.01 – 1.26), $P < 0.001$) increased the risk of relapse in patients initiated on a LAI (see table 3, also displaying the effects of the remaining explanatory variables).

The increased HR for the psychiatric co-morbidity score resulted in a sensitivity analyses investigating all components included in the psychiatric co-morbidity score as explanatory variables in a post-hoc defined Cox regression model showing that a diagnosis of an affective disorder (HR 1.13, 95% CI (1.05 – 1.23), $P < 0.005$), as well as a diagnosis of a substance misuse disorder (HR 1.11, 95% CI (1.03 – 1.19), $P < 0.01$)) was associated with relapse in patients initiated on LAI (table 4).

No new safety signals were discovered in this research which was in line with the expectations given the method and data sources used.

4. Discussion

In the current study, we showed that patients initiating second generation antipsychotic LAIs had a time adjusted reduction in the number of relapses of approximately 35-40 percent with a similar reduction in number of admissions to psychiatric hospital as compared to the period before initiating the treatment. Likewise, in hospitalized patients, the number of days hospitalized was reduced with 85 percent. As a consequence, the costs associated with hospital-based psychiatric treatment of patients decreased to approximately one quarter in the periods investigated after initiation of second generation antipsychotic LAI as compared to periods before initiation.

In the Cox regression model we showed that in patients initiated on LAI, age at diagnosis and a later calendar year of diagnosis were associated with a lower risk of relapse, whereas a higher number of previous admissions, a higher number of previous psychiatric bed days and a higher number of previous outpatient contacts, as well as psychiatric comorbidity and a diagnosis of cardiovascular disease were associated with an increased risk of relapse. The post-hoc defined Cox regression model applied to the same population including all components from the psychiatric comorbidity score showed similar results as the initial model, but additionally that a diagnosis of an affective disorder as well as a substance misuse diagnosis resulted in an increased risk of relapse.

Previous RCTs comparing LAIs antipsychotics to oral antipsychotic drugs have failed to show any significant difference between the two formulations on proxy markers of relapse or time to all-cause discontinuation (Kishimoto et al., 2014), contrasting the current findings of a reduction on all outcome measures, except from

intentional self-harm. The main reasons for similar outcomes in LAI and oral antipsychotic drug treated patients in RCTs are most likely a consequence of the RCTs themselves. In RCTs adherence to medication is optimized by e.g. frequent clinical assessments and by excluding patients who have somatic co-morbidity, psychiatric comorbidity like substance misuse or are otherwise unstable (Alphs et al., 2014). These characteristics were all linked to relapse in the current study and they are most likely also linked to a reduced adherence to treatment (Alphs et al., 2014; Nordon et al., 2017). Furthermore, in contrast to RCTs, observational studies like mirror-image studies, in which LAI is chosen by the clinician on the basis of patient´s behavior like non-adherence, have shown a significant reduction in relapse (Kishimoto et al., 2013). Such studies generally do not use rating scale determined proxy markers of relapse, but instead use objective measures like number of hospitalizations which are more relevant to clinicians (Alphs et al., 2014). The results from the current study showing a reduction in number of hospitalizations of approximately 0.57 is in line with a meta-analysis from Kishimoto et al (Kishimoto et al., 2013) based on 25 mirror-image studies, which showed a reduction in number of hospitalizations of 0.38. A recent small study by Vincent et al (Vincent et al., 2017) investigating paliperidone palmitate showed a reduction in admissions to approximately one third after LAI initiation, but with no difference in days hospitalized. Similarly Mesones-Peral et al (Mesones-Peral et al., 2017) also recently found reductions in admissions and bed days associated with paliperidone palmitate . Lastly, Souaiby et al (Souaiby et al., 2017) investigated the effects of combining LAIs to clozapine treatment in patients diagnosed with schizophrenia or schizoaffective disorder showing a reduction in admissions of approximately 60 percent and a reduction in bed days of approximately 83 percent in the year following LAI initiation. Combined, the three latest studies and the meta-analysis, included less patients than the current study, which by including a nationwide study population adds to the generalizability to clinical practice of the overall findings (Kukull and Ganguli, 2012). A newly published nationwide study utilizing a Cox regression model also showed similar results with HR for relapse of approximately 0.25 in incident patients diagnosed with schizophrenia treated with both first and second generation antipsychotic LAI as compared to remaining patients, albeit results not directly comparable due to the differences in methodology (Taipale et al., 2017).

In patients treated with LAIs, non-compliance and discontinuation of treatment has often been an indication for LAI treatment (Kishimoto et al., 2013). The study by Attard et al showed a high first year continuation of LAI after initiation (Attard et al., 2014). In the current study, we did not specifically investigate the attrition rate, but showed that the 2,233 patients being treated for the first six months was reduced to 1,383 patients treated for 12 months and 713 treated for 24 months, which could be caused by lack of retro- or prospective follow-up or discontinuation of treatment.

If ingested, an oral antipsychotic drug has the same or a similar active component as the corresponding LAI, with the differences being due to different pharmacokinetic properties, resulting in a slow and constant release of the active compound over several weeks and, consequently, a more stable plasma concentration in LAI treated patients. However, in RCTs a stable plasma concentration per se has not been demonstrated to be associated with significantly better efficacy or less side effects as compared to a less stable plasma concentration (Kishimoto et al., 2014; Ostuzzi et al., 2017). The potential benefit of treatment delivered by LAI in contrast to oral antipsychotic agents therefore most likely lies in the removal of daily adherence issues, and in clinicians potentially being made aware early if patients do not receive treatment, resulting in a potentially diminished risk of relapse as compared to oral treatment in which patients can be intermittently non-adherent without this is detected by the clinician resulting in an increased risk of relapse (Bossie et al., 2015). Additionally, even though a LAI is discontinued for longer periods of time, an emergent relapse will be substantially delayed as compared to the situation where an oral agent is discontinued.

As to our findings that a diagnosis of a co-morbid affective disorder, a co-morbid substance misuse disorder, or a diagnosis of a cardiovascular disease was associated with an increased risk of relapse, substance misuse has previously been linked to an increased risk of relapse (Porcelli et al., 2016). In RCTs, co-morbid psychiatric disorders are often an exclusion criterion, and in observational studies affective disorders co-morbid to schizophrenia have not been linked with relapse as an outcome previously (Bowtell et al., 2017; Porcelli et al., 2016). The finding of an association between relapse and cardiovascular disease is novel, and to further elucidate this, studies with other designs could be conducted.

When the potential reduced costs associated with LAI treatment utilizing standardized mean costs per bed day in a Danish psychiatric hospital were calculated, a clear reduction in costs due to a reduction in days hospitalized could be demonstrated. In the current study we did not include costs for outpatient contacts, contacts to general practitioners, costs associated with treatment of physical diseases or cost of antipsychotic drug treatments. Previous studies have shown that the main direct cost associated with treatment of schizophrenia is hospitalizations, closely followed by antipsychotic drug treatment and several types of outpatient treatment components (Knapp et al., n.d.; Zhu et al., 2008). The indirect costs associated with schizophrenia are harder to determine and consists of many components including unemployment, reduced productivity if employed, caregivers and family having a reduced productivity and premature mortality (Knapp et al., n.d.; Rosenberg, n.d.). Most other studies have calculated the economic effects of prescribing second generation LAIs, which most often are more expensive than the similar oral treatment option, in conjunction with the reduced costs of hospitalization, showing a positive economic effect of LAI treatment (Correll et al., 2016). Contrary to previous studies which have mainly had a short follow-up period, and a general short study period, we chose to include patients over an 18-year period with up to a total of four-year mirror period. Over this time-period, it would be difficult to calculate the specific costs associated with antipsychotic treatment as prices would vary and no formal register thereof exists. As a result we have chosen only to incorporate a simple economic calculation based on direct costs associated with hospitalizations.

Aripiprazole LAI was marketed in Denmark from late 2013 and paliperidone palmitate LAI three months, i.e. after the study period, therefore no patients were exposed to these drugs in the current study.

4.1. Strengths and limitations

The mirror image model primarily used in this study does carry some methodological weaknesses, for which it is not possible to adjust. The initiation of a LAI antipsychotic drug is not a random event, and is most often initiated at a certain time-point due to a specific cause, e.g. low adherence to treatment, multiple relapses and hospitalizations, substance misuse, intentional self-harm, which all would bias result towards better outcomes after LAI initiation, due to regression towards the mean of number of relapses, number of

hospitalizations, and number of bed days in the period after LAI initiation. This bias will be most profound for the time immediately before and after LAI initiation, and the effect would most likely diminish over time, making the results of the longer mirror-image periods less sensitive to this bias. Similar to this would be a specific expectation bias, since patient, relatives, and clinician would expect an improvement to occur after LAI initiation, which could cause a delayed referral or treatment seeking of patients towards psychiatric treatment. However, a reduced use of hospitalization and help seeking immediately after initiation of LAI would be expected, so again, most likely this would not affect the results from the longer mirror-image windows. Contrary to this, the use of an LAI would result in an immediate warning being given to the clinician if a patient was non-adherent to an LAI in contrast to oral treatment, which would result in a bias towards admission and hospitalization, biasing our results in a conservative manner. From a pure methodological view point, the main strength of the mirror-image design is the elimination of genetic, personality, and other stable characteristics for each patient biasing results, which would have occurred in a case-control design. The main weakness, general for all observational studies, is that no causal inferences can be made.

The 913 days of delay in patients diagnosed in the period 2008 and onwards could result in differences between patients diagnosed early in the study period as compared to later, but the sensitivity analysis did not show any significant effects on outcomes.

In conclusion, our findings show a reduction in number of relapses, number of admissions, days hospitalized if admitted, and as a result lowered costs after LAI initiation. These findings are similar to those of previous smaller studies conducted over shorter time periods investigating prevalent cases diagnosed with schizophrenia initiating LAI. Contrary to the previous studies we used a nation-wide population of newly diagnosed patients increasing generalizability by including all diagnosed patients and by including patients over an 18-years period. These population-based findings strongly support the use of LAI second generation antipsychotics in patients newly diagnosed with schizophrenia, although the design does not allow causal inferences.

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Demographics	**Total**		**Male**		**Female**	
Mean age at diagnosis ±SD (years)	33.61	12.70	32.22	11.49	35.72	14.10
Mean age at LAI ±SD (years)	36.58	13.34	35.15	12.12	38.75	14.74
Mean psychiatric comorbidity score (95%CI)	2.34	(2.33-2.36)	2.31	(2.28-2.31)	2.40	(2.37-2.43)
Long acting injectable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Olanzapine	5455	(52%)	3508	(55%)	1947	(47%)
Risperidone	4580	(44%)	2578	(41%)	2002	(48%)
Paliperidone	474	(5%)	272	(4%)	202	(5%)
Aripiprazole	-	-	-	-	-	-

Table 1: Demographics of study population

	6 month mirror-image analysis (N = 2233)						
	Mean before	**95% CI**		**Mean after**	**95% CI**		***Adj.Effect.***	***P***
Variable								
# relapse	1.08	1.01	1.14	0.64	0.58	0.71	0.60 (IRR)	< 0.001
# psychiatric admissions	0.82	0.76	0.87	0.48	0.42	0.54	0.59 (IRR)	< 0.001
# psychiatric bed days	68.40	65.45	71.36	10.37	9.14	11.59	-58.04	< 0.001
# intentional self-harm contacts	0.04	0.03	0.06	0.04	0.02	0.06	0.92 (IRR)	0.67
Hospital costs (in 1,000 Danish kroner)	145.32	136.11	154.52	33.40	30.15	36.65	-111.92	< 0.001
	12 month mirror-image analysis (N = 1383)							
	Mean before	**95% CI**		**Mean after**	**95% CI**		***Adj.Effect.***	***P***
Variable								
# relapse	1.69	1.56	1.82	1.09	0.93	1.24	0.64 (IRR)	< 0.001
# psychiatric admissions	1.37	1.26	1.49	0.83	0.70	0.96	0.60 (IRR)	< 0.001
# psychiatric bed days	118.49	111.48	125.49	18.82	16.15	21.49	-99.67	< 0.001
# intentional self-harm contacts	0.08	0.05	0.11	0.06	0.03	0.10	0.80 (IRR)	0.41
Hospital costs (in 1,000 Danish kroner)	261.51	240.34	282.68	62.82	55.24	70.40	-198.69	< 0.001
	24 month mirror-image analysis (N = 713)							
	Mean before	**95% CI**		**Mean after**	**95% CI**		***Adj.Effect.***	***P***
Variable								
# relapse	2.68	2.40	2.96	1.72	1.42	2.01	0.64 (IRR)	< 0.001
# psychiatric admissions	2.16	1.93	2.39	1.37	1.03	1.72	0.64 (IRR)	< 0.001
# psychiatric bed days	195.88	178.70	213.05	32.26	26.11	38.42	-163.62	< 0.001
# intentional self-harm contacts	0.13	0.06	0.19	0.12	0.04	0.20	0.93 (IRR)	0.81
Hospital costs (in 1,000 Danish kroner)	471.59	418.95	524.23	113.99	95.85	132.13	-357.60	< 0.001

Table 2: Mirror image analysis with 6, 12 and 24 months of pre- and post-LAI initiation study period. The effect size is represented by the coefficient of a linear regression analysis unless otherwise specified. IRR: Incidence rate ratio.

	HR	95%CI		*P*
Age at diagnosis	0.99	0.98	0.99	**< 0.001**
Sex	1.04	0.97	1.12	0.281
Calendar year of diagnosis	0.99	0.98	1.00	**< 0.05**
# of psychiatric admissions	1.02	1.01	1.02	**< 0.001**
# of psychiatric bed days	1.00	1.00	1.00	**< 0.05**
# of outpatient contacts	1.00	1.00	1.00	**< 0.001**
Psychiatric comorbidity score	1.07	1.04	1.11	**< 0.001**
Diagnosis of cardiovascular disease	1.12	1.01	1.26	**< 0.05**
Diagnosis of diabetes	0.87	0.70	1.09	0.235
Diagnosis of COPD	0.88	0.60	1.28	0.495
Diagnosis of hepatitis	1.27	0.91	1.78	0.162

Table 3: Cox regression model with relapse as outcome. HR: Hazard rate ratio. CI: Confidence interval. #: number of. COPD: Chronic obstructive pulmonary disease.

	HR	95%CI		P
Age at diagnosis	0.99	0.98	0.99	**< 0.001**
Sex	1.05	0.97	1.13	0.281
Calendar year of diagnosis	0.99	0.98	1.00	**< 0.05**
# of psychiatric admissions	1.02	1.01	1.02	**< 0.001**
# of psychiatric bed days	1.00	1.00	1.00	**< 0.05**
# of outpatient contacts	1.00	1.00	1.00	**< 0.001**
Psyciatric comorbidity	**HR**	**95%CI**		***P***
Diagnosis of psychosis	omitted			
Diagnosis of affective disorder	1.13	1.05	1.23	**< 0.005**
Diagnosis of substance misuse	1.11	1.03	1.19	**< 0.01**
Other psychiatric diagnosis	1.03	0.96	1.11	0.431
Diagnosis of intentional self-harm	0.98	0.86	1.12	0.798
Somatic comorbidity	**HR**	**95%CI**		***P***
Diagnosis of cardiovascular disease	1.12	1.01	1.26	**< 0.05**
Diagnosis of diabetes	0.85	0.68	1.06	0.148
Diagnosis of COPD	0.88	0.60	1.28	0.495
Diagnosis of hepatitis	1.27	0.91	1.78	0.162

Table 4: Post-hoc defined Cox regression model with relapse as outcome. HR: Hazard rate ratio. CI: Confidence interval. #: number of. COPD: Chronic obstructive pulmonary disease.

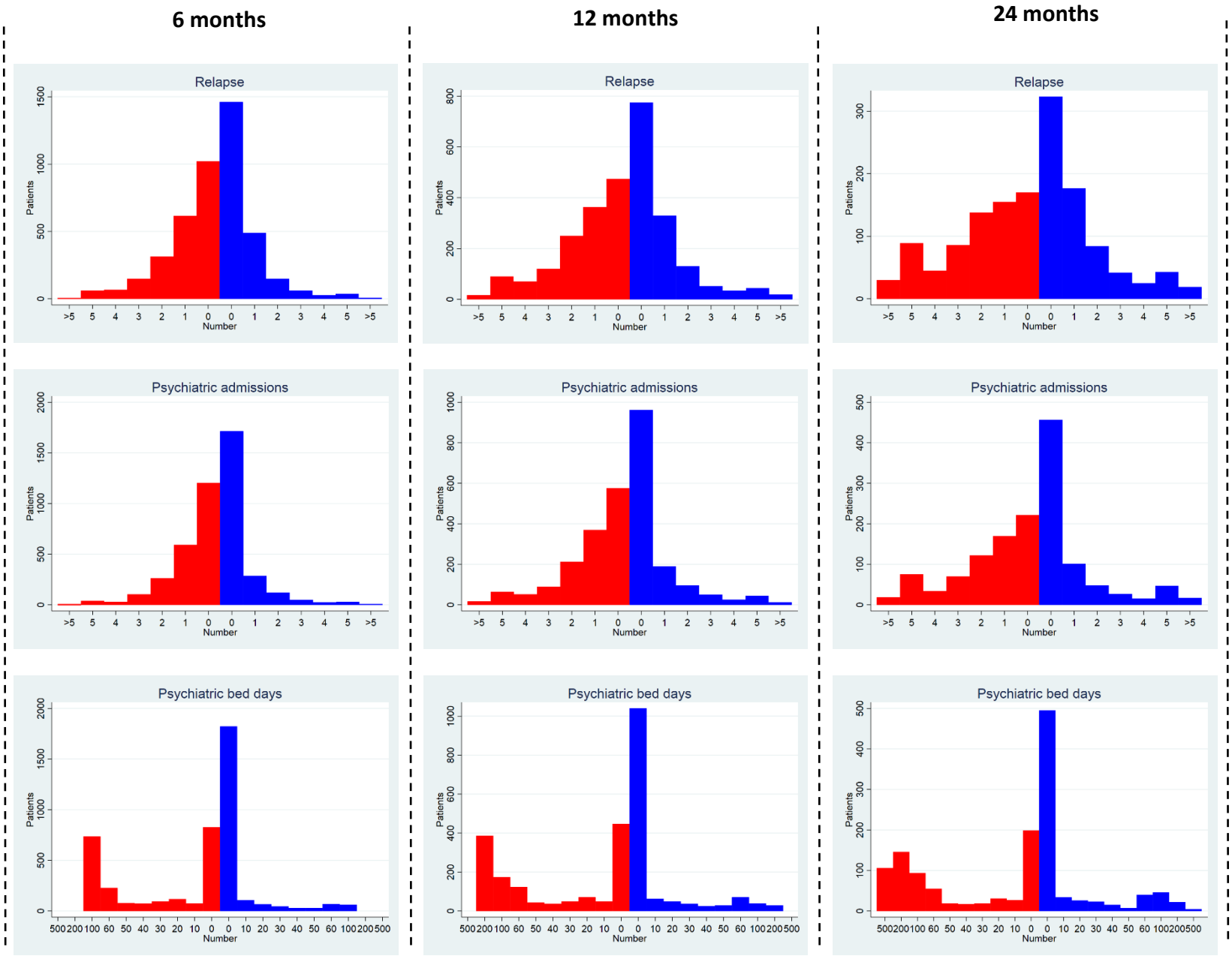
6 months
12 months
24 months
Relapse
Psychiatric admissions
Psychiatric bed days
Patients
Number

Figure 1: Frequencies of relapse, psychiatric admissions and psychiatric bed days before (left side) and after (right side) initiation of long action injectable antipsychotics