

Article

Use of Long-Acting Injectable Antipsychotics in Inpatients with Schizophrenia Spectrum Disorder in an Academic Psychiatric Hospital in Switzerland

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Abstract: Long-acting injectable antipsychotics (LAIs) offer many benefits to patients with schizophrenia spectrum disorder (SSD). They are used with very different frequencies due to questions of eligibility or patients' and prescribers' attitudes towards LAI use. We assessed the prescribing rates of LAIs in a large academic psychiatric hospital with public service mandate in Switzerland and compared them with other countries and health care systems. To our knowledge this study is the first to investigate the inpatient LAI-use in Europe. Medical records of all patients diagnosed with SSD discharged from the Clinic of Adult Psychiatry of the University Hospital of Psychiatry Zurich over a 12-month period from January to December 2019 were evaluated regarding the prescribed antipsychotics at the time of discharge. The rates of use of LAIs among all patients and among patients receiving LAI eligible antipsychotic substances were assessed retrospectively. We assessed records of 885 patients with SSD. Among all cases 13.9% received an LAI. Among patients who received antipsychotic medication that was eligible for LAI use (n=434) 28.1% received an agent as LAI. LAI use included paliperidone palmitate (69.9%), aripiprazole monohydrate (14.6%), risperidone (4.9%) and first-generation LAIs (9.8%). Compared to international frequencies of LAI administration, the prescription rate of LAIs in SSD patients was low. Further studies will evaluate patient- and prescriber-related reasons for this low rate.

Keywords: long-acting injectable; antipsychotic; depot; schizophrenia spectrum disorder; schizophrenia; schizoaffective; inpatient; prescribing pattern

1. Introduction

Long-acting injectable antipsychotics (LAIs) emerged as an important and effective treatment option for patients with schizophrenia spectrum disorders (SSD) including schizophrenia, particularly effective in reducing hospitalization [1]. In the US among all patients receiving an antipsychotic agent eligible for LAI use 4-28% receive their agent as LAI [2-4].

LAIs have initially been developed to improve adherence in patients suffering from SSD. However, recent clinical studies suggest additional advantages [5]. First, the prescription of LAIs is associated with better adherence in a randomized controlled trial and a retrospective analysis [6,7]. For instance, a recent meta-analysis of prospective and retrospective cohort studies has found that the risk for all cause discontinuation was lower in patients receiving LAIs than in patients receiving oral antipsychotics (OAPs) [1]. Second, patients treated with LAIs are at lower relapse risk compared to patients receiving OAPs in a meta-analysis of randomized trials [8]. Third, LAIs provide prolonged sustainable antipsychotic effects even if discontinued as shown in a recent re-analysis of

five placebo-controlled randomized trials where the time to relapse after discontinuation of medication was significantly longer in patients receiving long-acting paliperidone palmitate than in those receiving paliperidone orally before discontinuation [9]. Fourth, LAIs significantly reduce the rate of hospitalizations according to a recent meta-analysis [10]. Thus, LAIs are not only clinically effective but also reduce medical costs as shown in a meta-analysis [11]. Another benefit of LAIs refers to lower risk of being arrested or incarcerated in patients treated with LAIs compared to OAPs in a randomized review board-blinded study [12]. Finally, evidence of a meta-analysis of randomized controlled studies suggests similar tolerability between LAIs and OAPs [13]. Possible disadvantages of LAIs include the fact that treatment cannot be stopped immediately in case of side effects or clinical indications of a switch to another agent as well as common risks and side effects of intramuscular injections. Also, in case of withdrawal of patients' acceptance the treatment cannot be discontinued immediately. However, a recent meta-analysis by Yaegashi et al. suggested that there was no significant difference in cessation of treatment due to withdrawal of consent comparing patients treated with LAI to those treated with oral antipsychotics [14]. Concerning side effects LAIs were associated with higher rates of akinesia, low density lipoprotein change and anxiety but showed a lower rate of prolactin change in a meta-analysis of randomized controlled trials comparing LAIs and OAPs [13].

Currently four second-generation antipsychotics are available as LAI formulation: risperidone, paliperidone, aripiprazole and olanzapine [15]. Availability varies between countries e.g. olanzapine LAI is not approved in some European countries including Switzerland. Among first-generation antipsychotics haloperidol, zuclopenthixol, fluphenazine, perphenazine and flupenthixol are available as LAI formulations [16].

In light of the current evidence LAIs seem a valuable treatment option for patients with SSD. Yet data regarding prescription patterns of LAIs and related temporal trends are required. In a large study with data from the French healthcare system it could be shown that the proportion of patients receiving LAIs among those receiving any antipsychotic medication increased over the years 2007 to 2014 from 8.9 to 9.6% regardless of diagnosis or treatment setting [17]. However, there is a lack of evidence about the frequency of LAIs prescription in an inpatient setting. Moreover, available data from the United States present substantial variation: for example, a study from 2015 suggested that only 9% of inpatients were prescribed LAIs within the first 30 days after a schizophrenia-related hospitalization using data from Medicaid programs from multiple US states [7]. Similar trends were obtained by Kishimoto et al. in an inpatient setting in New York City [18]. On the other hand, in a hospital mainly serving low-income and uninsured population in Brooklyn, New York City, authors reported that 44% of inpatients were treated with LAIs at time of discharge [19]. Beside these three studies there are to our knowledge no other data evaluating the use of LAI in acute psychiatric inpatient settings; additionally, none of these studies analyzed LAI prescription rates in Europe. In a randomized clinical intervention trial it could be shown that LAI focused staff training potentially enhances the use of LAIs (91.0% in the intervention group vs. 51% in clinician's choice treatment) [20,21].

The aim of this descriptive retrospective study was to assess prescription rates of LAIs in a large academic psychiatric hospital in Switzerland. The University Hospital of Psychiatry Zurich is a public hospital with a service mandate for psychiatric care in a mixed urban and rural region covering approximately 500.000 inhabitants. Part of the service mandate is to provide treatments for all acute and chronic psychiatric disorders. As part of the Hospital the Clinic of Adult Psychiatry (Department of Psychiatry, Psychotherapy and Psychosomatics) offers psychiatric inpatient units for acute admissions.

2. Materials and Methods

We conducted a retrospective analysis of inpatients with SSD treated in the University Hospital of Psychiatry Zurich and assessed the rates of LAI use in this group. As part of clinical routine diagnoses were provided using ICD-10 criteria. All patients with a WHO-ICD-10 Chapter F2 SSD were included: schizophrenia (F20), schizotypal disorder (F21), delusional disorder (F22), brief psychotic episode (F23) and schizoaffective disorder (F25). Hereby all patients with SSDs receiving antipsychotic substances that are available for LAI use in Switzerland were included regardless of prior hospitalizations, time since onset of the disease or possible contraindications.

Data from all patients diagnosed with SSD discharged from the Clinic of Adult Psychiatry of the University Hospital of Psychiatry Zurich over a 12-month period from January until December 2019 were included. Patients' data were retrospectively reviewed and psychiatric diagnoses and prescribed antipsychotic medication at time of discharge from hospital were assessed.

In the prescribed discharge medication antipsychotics were evaluated in terms of availability as LAI formulation approved in Switzerland and thereby classified as "eligible" or "not eligible". The eligible substances were risperidone, paliperidone, aripiprazole, haloperidol, zuclopenthixol and flupenthixol. We rated, whether the substances if eligible were prescribed orally or administered as LAI formulation.

The project was approved by the Ethics Committee of the Canton of Zurich (BASEC-Nr. Req-2021-00376).

Statistical analyses were carried out using SPSS 27 (IBM). We performed a descriptive analysis of the sample regarding age, sex, diagnostic subgroups, comorbid substance use disorders, length of stay, and LAI prescription rate and type. Frequencies and proportions of above-mentioned demographic and clinical data were calculated.

Among all patients the two groups of patients receiving LAIs vs. patients receiving oral antipsychotics were compared with regard to age and length of stay using two-sample t-test and concerning the categorical variables gender and presence of substance use disorder using Chi square test (χ^2).

3. Results

A total of 2203 records of inpatients were screened, of which 40.2% (n=885) were diagnosed with SSD and enrolled in the study; 62.9% (n=557) of all patients diagnosed with SSD were male, and 37.1% (n=328) were female. The mean age was 40.51 years (SD 12.44). 89.7 % (n=794) of all 885 patients enrolled were prescribed an antipsychotic medication at discharge. 49.0% of patients (n=434) were treated with an antipsychotic agent that is both available for oral and LAI administration (classified as "eligible" for LAI use). Among those 434 patients 28.1% (n=122), received LAI antipsychotics. Additionally, one patient (n=1) received olanzapine LAI as off-label use. In total 13.9% (n=123) of all SSD cases, received an LAI. Among the group of patients receiving an LAI 69.9% (n=86) were treated with paliperidone palmitate, 14.6% (n=18) with aripiprazole monohydrate, 4.9% (n=6) with risperidone microspheres and 9.8% (n = 12) with a first-generation LAI. One patient (0.8%) received olanzapine pamoate as off-label as it is not approved in Switzerland. The characteristics of the patients and of the diagnoses and the prescribed medications in the respective diagnostic subgroups are summarized in table 1. The highest rates of LAI prescription were found in patients diagnosed with a schizoaffective disorder (16.0%, n=25), followed by the patients diagnosed with schizophrenia (15.5%, n=91) who represented the largest subgroup in our sample (66.2% of all patients, n=586). In the other subgroups LAIs were prescribed less often, and none of the 5 patients with a schizotypal disorder received an LAI. The patients receiving LAIs were significantly younger compared to non-LAI-treated patients (36.87 SD 11.53 vs. 41.09 SD 12.49 years, $p<0.01$) and there were more males among the LAI-treated patients (74.0% n=91 vs. 61.2%, n=466, $p=0.006$) (table 2). Furthermore, among patients with LAIs there were significantly more patients diagnosed with any comorbid substance use disorders compared to patients without LAIs (56.9% vs. 33.9%, $p<0.01$). Among the 123 cases receiving an LAI in 57%

(n=70) the LAI was prescribed prior to hospitalization, whereas in 43% (n=53) of patients LAI was newly started during the current hospitalization. Patients with LAI newly started compared to patients with no LAI had a mean age of 36.51 vs. 41.09 years ($p=0.01$) a length of stay of 37.28 vs. 24.08 days ($p<0.001$), a number of hospitalizations of 9.55 vs. 9.91 ($p=0.859$) and a time since first admission of 7.93 vs. 8.60 years ($p=0.559$). Patients with LAI newly started compared to patients without LAI were more frequent male (67.9% vs. 61.1%; $p=0.011$) and a substance use disorder was more frequent (39.6% vs. 33.9%; $p<0.001$).

Table 1. Demographic and clinical data.

	All SSD 100% (n=885)	Schizophrenia 66.2% (n=586)	Schizoaffective disorder 17.6% (n=156)	Brief psychotic episode 13.2 % (n=117)	Delusional disorder 2.4 % (n=21)	Schizotypal disorder 0,6 % (n=5)
Age, years (mean, SD)	40.51 (12.44)	40.21 (12.27)	44.25 (11.78)	35.54 (11.83)	50.10 (12.14)	34.60 (14.54)
Gender, m/ f (% , n)	m: 62.9% (n=557) f: 37.1% (n=328)	m: 67.2% (n=394) f: 32.8% (n=192)	m: 55.8% (n=87) f: 44.2% (n=69)	m: 54.7% (n=64) f: 45.3% (n=53)	m: 42.9% (n=9) f: 57.1% (n=12)	m: 60.0% (n=3) f: 40.0% (n=2)
Number of hospitalizations (n, mean, SD)	10.6 (15.25)	11.5 (15.77)	15.2 (17.08)	1.9 (2.03)	3.5 (4.14)	3.8 (5.22)
Time since first admission, years (mean, SD)	8.7 (8.05)	9.3 (7.86)	12.3 (8.22)	2.0 (3.71)	3.5 (5.58)	5.3 (7.55)
Antipsychotic medication (% , n)	89.7% (n=794)	92.7% (n=543)	91.7% (n=143)	80.3% (n=94)	52.4% (n=11)	60.0% (n=3)
Medication eligible for LAI use (% , n)	49.0% (n=434)	50.7% (n=297)	47.4% (n=74)	44.4% (n=52)	42.9% (n=9)	40% (n=2)
LAI (% , n)	13.9% (n=123)	15.5 % (n=91)	16.0 (n=25)	5.1% (n=6)	4.8% (n=1)	0.0% (n=0)
Paliperidone (% of LAI, n)	69.9% (n=86)	64.8 % (n=59)	88 % (n=22)	83.3 % (n=5)		
Aripiprazole (% of LAI, n)	14.6% (n=18)	14.3 % (n=13)	12 % (n=3)	16.7 (n=1)	100 % (n=1)	
Risperidone (% of LAI, n)	4.9% (n=6)	6.6 % (n=6)				
First-generation antipsychotic (% of LAI, n)	9.8% (12)	13.2 % (n=12)				
Olanzapine (% of LAI, n)	0.8% (1)	1.1 % (n=1)				

¹ Demographic and clinical data of the total sample and diagnostic subgroups are shown: f: females; m: males; LAI: long-acting injectable; SD: standard deviation; SSD: schizophrenia spectrum disorders; Mean Age in years, percentage (%) and total number (n) of men and women, percentage (%) and total numbers (n) of fractions of antipsychotic medication as well as LAI eligible antipsychotic medication. Below percentage (%) and total number (n) of patients receiving an LAI are shown. Among patients receiving an LAI distribution of used LAI agents in total sample and diagnostic subgroups is shown in percentage (%), and total number of patients (n).

Table 2. Group comparisons.

	LAI (n=123)	Non-LAI (n=762)	Statistical test	p-value
Age, years (mean, SD)	36.87 (11.53)	41.09 (12.49)	t=3.516	<0.01
Gender, m/ f (% , n)	m: 74.0% (91)	m: 61.2% (n=466)	$\chi^2=7.472$	0.006

	f: 26.0% (32)	f: 38.8% (n=296)		
Substance use disorder (%, n)	56.9% (n=70)	33.9% (n=258)	$\chi^2=24.13$	<0.01
Length of stay, days (mean, SD)	27.95 (33.78)	24.08 (25.89)	$t=-1.47$	0.142
Number of hospitalizations (n, mean, SD)	15.12 (19.25)	9.91 (14.39)	$t=-2.876$	0.005
Time since first admission, years (mean, SD)	9.39 (7.63)	8.60 (8.11)	$t=1.010$	0.313

² Group comparisons: Statistical tests were performed to compare patients receiving an LAI with those not receiving an LAI. f: females; m: males; LAI: long-acting injectable; SD: standard deviation. Two sample t-tests were performed for interval-scaled variables, Pearson Chi square tests were performed for categorical data. Mean age in years (a) and standard deviation (SD), percentage (%) and total number (n) of men and women, percentage (%) and total numbers (n) of fractions of antipsychotic medication as well as LAI eligible antipsychotic medication.

4. Discussion

In our sample the prescription rate for LAI antipsychotics in patients with SSD is lower than reported elsewhere. Patients receiving LAIs are predominantly male and younger than those who are not prescribed an LAI.

28.1% of the patients treated with an antipsychotic substance that is available as LAI were treated with an LAI. While this rate seems rather promising one has to consider that taken together only 13.9% of all patients with SSD were treated with an LAI which appears rather low. The LAI prescribed most often was by far paliperidone palmitate followed by aripiprazole monohydrate while risperidone microspheres and first-generation LAI were prescribed in a small patient subgroup. These results are in contrast with the findings of Olayinka et al. [19] who assessed LAI prescription rates in an inpatient setting and reported that 44% of a total of 43 patients with SSD were treated with an LAI. They found risperidone microspheres to be the most often used substance followed by paliperidone palmitate and haloperidol decanoate. In a study by Kishimoto et al. in an inpatient setting [18] 32.9 % of the patients were found to be discharged on an LAI. Similar results were found in another large study of 2009 by Barnes et al. [22] where 35% of 2032 acute inpatients and 28% of a forensic patient sample were found to be treated with an LAI. As a limitation one has to note that in those times most commonly first-generation antipsychotic LAIs were used and risperidone microspheres was the only available second-generation antipsychotic LAI. A potential reason underlying the differences regarding LAI prescription rates estimated in our sample and other studies such as for example the study of Olayinka et al. in Brooklyn, New York, [19] maybe associated with differences in the socio-economic status of the patients included and the healthcare system. In fact, there is also a considerable difference for the duration of hospitalization (24.62 days average length of stay in our study vs. 14 days in the study by Olayinka et al. [19]). In Switzerland the longer lengths of stay could be used for longer discussing the advantages and disadvantages of LAIs. A possible reason for the higher LAI prescription rates in Brooklyn might be leaning more to a recommendation of LAI use. In relation to counselling on LAI use it is well known that the prescriber's and patient's attitude in terms of LAIs might influence the rate of LAI and that stigmatization and prejudices of LAI can be reduced by well-informed shared-decision making [23-26]. Common negative factors are the prescriber's attitude that LAI might not be suitable for treatment of first psychosis [24] while the opposite could be proven [27]. Another point is the fact that the selected agent is not eligible for LAI use [24]. The second point might partly explain the apparently low rate of LAI-use in our study. In Switzerland olanzapine which is in our sample the

most used antipsychotic substance (29.5% of all patients with antipsychotic medication) is not available for LAI use while it is largely available in other parts of the world including the US and UK. If olanzapine pamoate was available in Switzerland in the study both the rate of patients treated with an eligible substance for LAI and probably also the rate of LAI use among all patients might have been higher. Other interesting findings in our study were that there were not only more male patients in the sample than female but also there were significantly more male patients receiving LAIs than female patients – findings that are in line with other studies [22,28]. Furthermore, patients receiving LAIs in our study were significantly younger compared to those not receiving LAIs indicating perhaps that in the recent years offering LAIs to patients has become more frequent as new substances came to market whereas older patients either aren't offered LAIs in the course of their illness or tend to refuse LAI use. They were also younger than seen in other studies [19,22].

43% of LAIs were newly installed during the assessed hospitalization. Since it can be assumed that a relevant part of the pre-installed 57% of LAI were also installed during a prior hospitalization, inpatient setting seems to be an important factor of LAI introduction in Switzerland. While inpatient setting allows LAI installation during an acute phase of treatment reducing rates of relapse and rehospitalization early LAI introduction in an outpatient setting might even preserve patient from any hospitalization [10] and should therefore be offered as early as possible.

It is also of particular importance that patients with comorbid substance use disorder were more frequently receiving an LAI as this group of patients is less adherent to therapy due to substance use [29].

As seen by the many advantages following LAI medication increasing the rate of LAI use seems to be desirable. Therefore, measures to increase the rate should be evaluated [30,31]. First, it seems useful to inform each patient who is treated with an eligible substance by default about the LAI availability, the many advantages and the convenience of the LAI formulation and thereby trying to motivate patients to think about an LAI use. It is to be assumed that this does not take place equally everywhere as not only patients but also clinician's attitude towards LAI is often burdened with prejudices as mentioned above. As shown in a recent study, a large number of early-phase schizophrenia patients accepts therapy with LAIs after being offered those and informed following a standardized study protocol [21].

Bringing these findings into clinical practice it has to be investigated whether the rate of LAI use could be increased by carrying out patient information and education in standardized form such as a brief information sheet or standardized interview as well as by training of clinicians what has already been proven to increase usage of LAI [20,21,32]. Second, from our point of view, the observed low rates of LAI prescription in the present sample may further stimulate the ongoing discussion whether the availability of a substance as LAI formulation should be a selection criterion for the initial choice of an antipsychotic substance at the beginning of a treatment [20,33-35]. And third, it would be crucial to develop new agents in LAI formulation but also increase efforts to develop LAI formulations for currently established compounds.

We state the following limitations: We provided numbers on patients being prescribed LAIs prior to hospitalization and patients newly started with LAIs during current hospitalization. However, we acknowledge that in patients receiving LAI before hospitalization we did not have data on whether medication with LAI was initiated in an outpatient setting or during a previous hospitalization. Therefore, a precise number of patients where LAI was newly installed in an in- or outpatient setting cannot be provided. Furthermore, we state that standardized data on the duration of illness was not available. However, we considered providing a potential surrogate of illness duration estimating time since first admission.

5. Conclusions

Only 13.9% of SSD inpatients received an LAI as opposed to 86.1% who did not. This rate is low in light of the evidence for improved relapse prevention. This can partly be attributed to the non-availability of LAI formulation of some agents. However, among patients receiving an agent eligible for LAI use still only 28.1% of the patients receive an LAI. The underlying reasons – patient or prescriber related – remain to be further evaluated. Further research is needed to evaluate if this rate might be increased by standardized information procedures or motivational interventions.

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Data Availability Statement: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest: GS has served as a consultant for HLS Therapeutics and Thermo Fischer. ES received in the last three years honoraria and grants for advise and educational lectures from Lundbeck Switzerland, Schwabe Switzerland and Germany, Janssen Switzerland, Otsuka Pharmaceutical Switzerland, Mepha Pharma Switzerland, Recordati Switzerland and Sunovion Pharma United Kingdom and Angelini. AB received speaking fees from Recordati. The other authors declare no conflicts of interest.

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