Schizophrenia Long-Acting Injectable Antipsychotic Initiation Index: A Clinician Rated Instrument for Improving Treatment in Schizophrenia

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Abstract

Background: Schizophrenia is a severe psychiatric condition with devastating consequences for the individual's functionality and leading to severe disability. Lack of insight and non-adherence to treatment remain the most important factors in the progression of the disease to chronicity.

Despite their proven effectiveness in preventing relapses, reducing morbidity and mortality, long acting injectable antipsychotics (LAIs) are still underused. One of the causes invoked is the lack of guidelines or protocols for initiating LAIs.

Objective: The aim of this article is to present Schizophrenia long-acting injectable antipsychotic initiation index (SLAI), a clinician-rated index that rates the important factors of the disorder across seven items: age, duration of illness, relapses, antipsychotic treatment response, family support, antipsychotic existing formulation and adherence.

Method: A retrospective study in which all patients with schizophrenia discharged on oral antipsychotics without LAIs treatment lifetime were evaluated with SLAI for opportunity for LAIs initiation.

Results: Of 225 consecutive patients, 144 patients (64%) had a strong indication for initiating LAI and 76 (34%) had moderate indication. 203 patients (90.2 %) had more than 2 relapses. The results of our research showed that 177 patients (78.7%) received at discharge an oral antipsychotic that also had a long-acting formula.

Conclusion: This paper proposed an instrument designed to improve treatment in schizophrenia using a simple conceptual model which integrates important predictors of good or poor outcomes.

1. Introduction

Schizophrenia is a severe psychiatric condition with devastating consequences for the individual's functionality and leading to severe disability [1, 2]. Lack of insight and non-adherence to treatment remain the most important factors in the progression of the disease to chronicity [3–5].

Despite their proven effectiveness in preventing relapses, reducing morbidity and mortality, LAIs are still underused [6–8]. The main causes of low utilization are related to the patient (fear of needles, stigma, desire not to be under control, etc.) but also to the clinicians (costs, personal beliefs or lack of experience) [9, 10]. One of the causes invoked by clinicians is the lack of guidelines or protocols for initiating LAIs. Because of this, initiation with LAIs is often delayed, or LAIs are used in severe forms of the disease or even in cases considered treatment-resistant [11, 12].

The development of an instrument for psychiatrists to provide a quick orientation on the opportunity to initiate treatment with LAI could improve adherence and outcome in schizophrenia.

2. Aims Of The Study

This paper describes an instrument called Schizophrenia long-acting antipsychotic initiation index – Schizophrenia Long-acting injectable antipsychotic Initiation Index), designed to improve initiation of LAIs. This index is a conceptual model, based on the continuous work over the past 20 years for a better adherence and outcome in schizophrenia.

3. Methods

3.1 Rationale for LAI initiation index

There are no initiation guidelines or protocols but only indications and suggestions from experts [13, 14]. Often psychiatrists consider that it is not yet the time, the patient could refuse LAI, the costs can be higher, the supervision must be more careful, thus delaying initiation.

The SLAI Index provided was developed by an experienced schizophrenia research group leading by Petru Ifteni, M.D., PhD, professor of psychiatry at Transilvania University of Brasov, Romania, Faculty of Medicine.

3.2 Description of the index

Schizophrenia long-acting injectable initiation index is a clinician-rated instrument that is scored using available clinical information for each of the seven domains. Each item is rated on a 3-point scale with 5 points, 3 points, and 1 point. Based on the patient’s data, the clinician will choose one value (e.g. age between 18 and 25 will be scored with 5 points) for all seven items. The final score is the sum of all seven items. SLAI is presented in table 1.

Table 1. Schizophrenia long-acting injectable antipsychotic initiation index

DOMAINS	Score
I. Age	
18-25 years	5 points
26-35 years	3 points
>35 years	1 point
II. Duration of illness	
2-5 years	5 points
6-10 years	3 points
>10 years	1 point
III. Relapse	
3 or more relapses	5 points
2 relapses	3 points
1 relapse	1 point
IV. Response to oral antipsychotic	
good response/remission	5 points
partial response	3 points
poor response/treatment-resistant	1 point
V. Patient social support	
2 or more family members	5 points
1 family member	3 points
no family member	1 point
VI. Antipsychotic formulation	

both oral and LAI	5 points
only oral	3 points
clozapine	1 point
VII. Treatment adherence	
non-adherence	5 points
partial adherence	3 points
good adherence	1 point

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3.3 Theoretical rationale for items

The index items are derived from consideration of important elements involved in the outcome of schizophrenia: age, duration of illness, number of relapses, antipsychotic treatment response, family support and adherence.

I. Age

The patient's age is a key factor in subsequent evolution. Young patients may still have many neurocognitive resources for treatment response, remission and recovery [15]. Thus, for the age between 18 and 25 years we gave 5 points, for the age between 26 and 35 years we gave 3 points, and for those aged between 36 and 45 years, we gave 1 point.

II. Duration of illness

Studies show that neuropathological changes occur in the first years of the disease [16]. Thus, the first 2–5 years can be considered to have major importance for the patient. We rated with 5 points for patients with a disease duration between 2 and 5 years, 3 points for a duration between 6 and 10 years and 1 point for a disease duration over 10 years.

III. Relapses

Relapses and hospitalizations in the early years are a prognostic factor for the unfavorable evolution towards cognitive decline and chronicity [17, 18]. Therefore, experts recommend the early initiation of LAI, after the first relapses caused by non-adherence. We rated with 5 points for at least 3 relapses, 3 points for 2 relapses and 1 point for 1 relapse.

IV. Response to oral antipsychotic

Many young people with schizophrenia respond well to the first trials with antipsychotics, a significant percentage even get remission [19]. Individual responsiveness, the severity of pathology are criteria that influence the choice of antipsychotic and doses. The therapeutic response decreases significantly with the increasing number of relapses [20]. We rated 5 points for complete therapeutic response/remission, 3 points for partial response (residual symptoms at effective doses of oral antipsychotic) and 1 point for lack of response and need for clozapine.

V. Family support

Family support is important as the other elements of therapeutic management [21]. In patients with adherence problems, the lack of family members involved in the therapeutic process is considered a predictor of therapeutic abandonment, even when initiating depot formulas.

The presence of 2 or more family members close to the patient was rated with 5 points, of a single member with 3 points and in situations where the patient is alone only 1 point.

VI. Antipsychotic existing formulation

If the patient received an OAP that also has LAI formulation (aripiprazole, olanzapine, risperidone, and paliperidone) we gave 5 points, if there is only the oral formulation (amisulpride and quetiapine) we gave 3 points and if the patient was on clozapine 1 point.

VII. Treatment adherence

Assessing adherence to treatment is a complex and subjective approach. Many methods have been proposed, none of which are perfect. In general, the patient with schizophrenia can be considered as adherent, partially adherent or non-adherent [22, 23]. In the patient's file, on admission, it is mentioned if the patient is adherent, partially adherent or non-adherent. The adherence was evaluated using Kemp's 7-point scale [24]. For the 3 variants listed, we rated 1 point for good adherence, 3 points for partial adherence and 5 points for poor adherence.

3.4. Scoring, interpretation and recommendations

All 7 items of the index have equal importance in the management of the patient with schizophrenia when LAI initiation has taken into account. The final score obtained could range from minimum of 7 points to a maximum of 35 points, placing the patient in one of the following categories:

25–35 points = strong indication for LAI initiation. This score indicates the need for **a preventive action**. It means that the patient has the premises (age, duration of the disease, support, therapeutic response) and the highest chances of total functional recovery. LAI should be initiated as soon as possible to prevent a new relapse or hospitalization.

15–23 points = moderate indication for LAI initiation. This score indicates the need for **a better functionality action**. It should be interpreted as a score in which the patient can benefit from LAI for

significant improvement in functioning and therefore a better social and professional integration.

07–13 points = low indication for LAI initiation. This score indicates the need for **a better autonomy action**. It means that long-acting treatment could increase patient' autonomy especially in the cases of patients with low support, low income or homeless.

The initiation index must be interpreted with few recommendations. In the case of patients with no relapse, there is still the possibility of therapeutic abandonment, so initiation is a preventive measure. In treatment-resistant schizophrenia, we have to decide if it is really a case of resistance or is in fact non-adherence. In the case of false treatment resistance situation, we recommend LAI initiation.

For patients on clozapine for treatment-resistance or for aggressive behavior switching to an LAI is not recommended. In cases of severe adverse events this switch must be done very carefully.

4. Methods

3.1 Setting, study design and measures

To assess the LAI initiation, we conducted a retrospective study in the Clinical Hospital of Psychiatry and Neurology in Brasov, an academic setting with 120 beds for acute patients. The inclusion criteria were the diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), aged 18–45 years, and no history of LAI treatment. The period was between 1 January 2010 and 31 December 2019.

The data included the age of onset of the disease, the duration of the disease, the number of relapses, the response to antipsychotic treatment, adherence to treatment, the number of family members with whom the patient lives and the available formulas of the antipsychotic with which the patient was discharged.

Clinical interviews, health and psychiatric records and chart reviews were used to collect participants' data. The scale used in this research were to assess adherence was Kemp's 7-point scale.

The study was approved by the local ethics committee.

3.3 Statistical analysis

For statistical analysis of the data, we used the Statistical Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA) software for Windows (version 21). Demographic, clinical, and treatment variables were compared using Chi Square Tests (categorical variables) or ANOVAs (continuous variables). All statistics were two-tailed.

4. Results

During the 10-year research period, 1116 different patients with schizophrenia were hospitalized. Of these, 477 (42.7%) met the age eligibility criteria (between 18 and 45 years). A total of 225 patients out of

477 (47.1%) with the mean age of 37.8 years (SD $\pm$ 5.9) had never had treatment with LAIs lifetime. Patients' characteristics are presented in Table 2.

Table 2
Demographics

Parameters	
Male gender (n; %)	52; 53.6 %
Age (mean, SD)	36.7; $\pm$ 5.6
Age group	
- 18–25 years (n; %)	1; 0.9%
- 26–35 years (n; %)	30; 30.9 %
- 36–45 years (n; %)	66; 68.2 %
Duration of illness (mean, SD)	12.4; $\pm$ 14.1
Duration of illness group	
- 2–5 years (n; %)	22; 22.7 %
- 6–10 years (n; %)	18; 18.6 %
- > 10 years (n; %)	57; 58.7 %
Relapses	
- 2 or more 2 relapses (n; %)	88; 90.7 %
- 1 relapse (n; %)	5; 5.2 %
- No relapse (n; %)	4; 4.1 %
Family support	
- 2 members or more (n; %)	36; 37.1 %
- 1 member (n; %)	40; 41.2 %
- No member (n; %)	21; 21.7 %
Response to oral AP	
- Good response (n; %)	56; 57.7 %
- Partial response (n; %)	40; 41.3 %
- No response (n; %)	1; 1 %
Adherence	
- Good (n, %)	13; 13.4 %
- Partial (n, %)	9; 9.3 %

Parameters	
- Non-adherence (n, %)	75; 77.3 %
No of antipsychotics used life time	
- 1 or 2 (n; %)	35; 36.1%
- 3 or 4 (n; %)	41; 42.2%
- 5 or more (n; %)	22; 22.7%

Using the index, we can get 15 score variants, between 7 and 35, only odd scores and different number of potential SLAI variants (Table3).

Table 3
Distribution of SLAI score

SLAI score variants	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35
Number of the potential variants	1	1	2	2	3	3	4	4	5	3	3	2	1	1	1

The scores obtained by the patients are presented in Fig. 1.

Most patients were young, 57 patients (25.3%) aged in the critical period of the disease (3rd decade of life, between 20 and 30 years) [25]. A significant number of patients in this age group had a maximum score at least 4 items indicating the need for LAI initiation. 203 patients (90.2 %) had more than 2 relapses. 105 patients (46.7 %) lived with at least one family member. 68% of patients was non-adherent which confirms that 2/3 of patients with schizophrenia are not treatment compliant (Table 4).

Table 4
The index items

Items	Score		
	5 points	3 points	1 point
age (n; years; %)	20; 8.9%	71; 31.5%	134; 59.6 %
duration of illness (n; years; %)	35; 15.6 %	84; 37.3 %	106; 47.1%
relapses (n; %)	203; 90.2 %	12; 5.3 %	10; 4.5 %
response to OAPs (n; %)	140; 62.2 %	78; 34.7 %	7; 3.1 %
family support (n; %)	84; 37.3 %	105; 46.7 %	36; 16 %
AP formulation (n; %)	177; 78.7%	43; 19.1%	5; 2.2%
adherence (n; %)	154; 68.4 %	55; 24.5 %	16; 7.1 %

The results of our research showed that 177 patients (78.7%) received at discharge an OAP that also had a long-acting formula. A well-known fact in Romania is the affinity of clinicians for olanzapine, an antipsychotic described as being efficient, cheap, affordable even for the uninsured patients, largely available and having a long-acting formulation. Olanzapine long-acting formula has the disadvantage of requiring post-injection monitoring for a period of 3 hours, which makes it difficult to initiate, (fact obvious in the current COVID-19 pandemic) [26]. The antipsychotic used at discharge are presented in Table 5.

Table 5
Antipsychotic used at discharge

Oral antipsychotics			Concomitant medication					
OAPs	n; %	Dose (mean, SD)	MS (n; %)	BZD (n; %)	ACh (n; %)	HYP (n; %)	AD (n; %)	2ndAP (n; %)
OLZ	124; 55.1%	15.3 mg; $\pm$ 4.7	102; 45.3%	116; 51.5%	28; 12.4%	20; 20.9%	4; 1.7%	23; 10.2%
QUE	25; 11.1%	550 mg; $\pm$ 151	17; 68%	15; 60%	6; 24%	-	-	3; 12%
CLO	5; 2.2%	300 mg $\pm$ 112	-	-	-	-	-	-
RIS	28; 12.4%	3.2 mg; $\pm$ 0.91	8; 28.6%	15; 53.6%	12; 42.9%	6; 21.4%	2; 7.1%	-
PAL	11; 4.9%	7.5 mg; $\pm$ 1.73	4; 36.4%	5; 45.5%	-	3; 27.3%	-	-
AMI	13; 5.8%	514 mg; $\pm$ 195	4; 30.7%	6; 46.1%	1; 7.7%	2; 15.4%	-	-
ARI	9; 4%	18 mg; $\pm$ 8.3	4; 44.4%	3; 33.3%	-	3; 33.3%	-	-
HAL	10; 4.4%	7,7 mg; $\pm$ 2.9	6; 60%	8; 80%	5; 50%	-	-	-
(OAPs = oral antipsychotics; OLZ = olanzapine; QUE = quetiapine; CLO = clozapine; RIS = risperidone; PAL = paliperidone; AMI = amisulpride; ARI = aripiprazole; HAL = haloperidol; MS = mood stabilizer; BZD = benzodiazepine; ACh = anticholinergic; HYP = hypnotic; AD = antidepressant; 2nd AP = concomitant use of a 2nd antipsychotic)								

Evaluation of patients with SLAI showed that 144 patients (64%) had a strong indication for initiating LAI and 36 (37.1%) had moderate indication. Five patients, discharged on clozapine, without previous long-acting treatment, was considered as having a low indication (Fig. 2).

Discussion

We have described the development and initial standardization of the 7- item SLAI as an instrument for measuring the need for LAI initiation in schizophrenia.

As far as we know, this is the first index created to encourage the initiation of LAI in schizophrenia, providing evidence to not delay this treatment.

Although many studies indicate that the use of LAIs may have the potential to prevent relapses and hospitalization compared with oral antipsychotic use [27], and although second-generation LAI formulations are widely available, it has been estimated that only 10-20% of eligible patients are actually prescribed LAIs [28]. The results obtained show that a significant number of patients who had an indication for LAI was discharged with OAPs.

One explanation for why these agents are under-initiated may be the current lack of clear and practical guidelines on how and to whom to initiate treatment with these agents. Studies show that initiation is common in severe patients, with involuntary hospitalizations, with evidence of non-adherence to treatment [29]. This could lead to a decline in LAI confidence.

Despite availability of all LAIs formulation in Romania, free of charge for insured patients with schizophrenia, a significant percentage of patients with a strong indication for LAIs (64%) were still discharged on OAP.

We must emphasize that the presence of a low score should not be a barrier in initiating LAI. The initiation of LAI in these patients if it is followed by all measures to ensure adherence (government programs, institutional support, etc.) can lead to reduced hospitalizations, direct and indirect costs and an acceptable degree of patient autonomy.

This index can also enhance the patient's collaboration and the family support of the treatment management because presenting the need for initiation score could build a strong confidence in the clinician's judgment.

With minimal time investment, patients and their families could become sufficiently informed to accept LAI initiation. It could also help psychiatrists working only in the outpatient department or in private practice to initiate LAI because this type of treatment is usually initiated in the hospital.

Like any instrument, the SLAI scale has several limitations. One limitation could be the application of this index to patients with concomitant medication which could rise or low the serum level of antipsychotic [30]. Another limitation would be the application of the LAI initiation index to young patients who are pregnant where initiation still raises widespread debate [31]. The present study design did not specifically address effectiveness of a proposed index. We report evaluation on the relatively small number of patients and preliminary experience with this index have been encouraging.

Should the validity of the SLAI be upheld by future studies and independent investigators, its use might be expected to promote uniformity and reliability in research findings.

Conclusion

This paper describes an index designed to improve treatment outcomes in schizophrenia and can be implemented in routine clinical management. SLAI has potential value in a wide range of settings. It can be used by clinicians in hospitals to argue the therapeutic decision, or in the outpatient department when evidence of non-adherence appears.

Abbreviations

LAIs: Long-acting injectable antipsychotics; SLAI: Schizophrenia long-acting antipsychotic initiation index; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; OAP: Oral antipsychotic

Declarations

Acknowledgements

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Availability of data and materials

Data is available from the corresponding author upon reasonable request.

Declarations

Ethics approval, guidelines and consent to participate

All participants provided written informed consent. This study was approved by the Ethics Committee of Hospital of Psychiatry and Neurology of Brasov, Romania. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

NA.

Competing interests

There is no conflict of interest for all authors.

Availability of data and materials

Data is available from the corresponding author upon reasonable request.

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Authors' contributions

IP and TA collected data, revised this manuscript; IP wrote this paper. All authors approved the publication of this manuscript.

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Figures

Figure 1

Distribution of possible scores and those obtained using SLAll.

Figure 2

Indication for LAI initiation (strong, moderate, and low).