



Rating Opportunity for Long-Acting Injectable Antipsychotic Initiation Index (ROLIN)

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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 Rating Opportunity for Long-Acting Injectable Antipsychotic Initiation Index (ROLIN), 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 ROLIN for opportunity for LAIs initiation.

Results: Of 225 consecutive patients, 126 patients (56%) had a strong indication for initiating LAI (score between 25 and 35). Kolmogorov-Smirnov test was used for checking the normal distribution of values (95% CI for the mean = 9.5781 to 20.4219; 95% CI for the median = 6.5920 to 24.8161; SD = 9.7907; Coefficient of Skewness = 0.0743; Coefficient of Kurtosis = -1.1377).

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.

Keywords: schizophrenia, antipsychotic, treatment, relapse, outcome, long-acting injectable

INTRODUCTION

Schizophrenia is a severe psychiatric condition with devastating consequences for the individual's functionality, leading to severe disability (1, 2). In addition, patients with schizophrenia have high levels of cardiovascular comorbidity (3) metabolic diseases (4), sudden death (5) and lower life expectancy (6).

According to a study published in 2016, schizophrenia contributes with more than 13 million life years lived with disability (YLDs) to burden of disease globally, equivalent to 1.7% of total YLDs globally (7).

Treatment non-adherence is the most important factor for the disease's progression. (8–10). Non-adherence has multiple causes related to illness (lack of insight, cognitive impairment, symptoms, etc.), patient (attitude toward medication, stigma, etc.), family (attitude toward symptoms, attitude toward medication and stigma), society (costs, treatment facilities, etc.), antipsychotic treatment (route of administration, number of administrations and side effects) (11).

It is unanimously accepted that sustained antipsychotic treatment is the only proven way to determine remission, maintain it and prevent relapses (12, 13).

Despite their proven effectiveness in preventing relapses, reducing morbidity and mortality, LAIs (long-acting injectable antipsychotics) are still underused (14–16). The main reasons for low utilization are patient-related (fear of needles, stigma, desire not to be under control, etc.) but also clinician-related (costs, personal beliefs or lack of experience) (17, 18). Besides these aspects, clinicians invoke the lack of guidelines or protocols for initiating LAIs. As a result, LAIs initiation is often delayed, or they are used in severe forms of the disease or even in cases that are considered treatment-resistant (19, 20).

Guidelines released by the American Psychiatric Association (APA) or authorities, organization and recommendation of experts from other countries to improve quality of care and treatment outcomes in patients with schizophrenia tend to have general consideration (21–23). There are no initiation guidelines or protocols regarding LAI treatment initiation, but only indications and suggestions from experts (24, 25). Often psychiatrists consider that “it is not yet the time” or “it is too early” or they consider that the costs are too high and the supervision must be more careful, thus delaying initiation.

Developing an instrument for psychiatrists, designed to provide quick guidance on the opportunity to initiate LAI treatment, could improve adherence and consequently the outcomes in schizophrenia.

This paper describes an instrument called Rating Opportunity for Long-Acting Injectable Antipsychotic Initiation Index (ROLIN), designed to improve initiation of LAIs in schizophrenia. ROLIN is a conceptual model, developed by an experienced schizophrenia research group led by Petru Ifteni, M.D., PhD, and professor of psychiatry at Transilvania University of Brasov, Romania, Faculty of Medicine. This clinician-rated instrument is scored using available clinical information for 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' scores (see Methods; **Table 1**).

METHODS

Study Design and Procedure

We conducted a retrospective study in the Clinical Hospital of Psychiatry and Neurology in Brasov, an academic setting with 150

TABLE 1 | Rating opportunity for long-acting injectable antipsychotic initiation index (ROLIN).

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

beds for acute psychiatric patients. The inclusion criteria were: diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), age between 18 and 45 years, and no history of LAI treatment. The assessed period was from January 2010 to 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, the adherence to treatment, the number of family members with whom the patient lives and the available formulations of the antipsychotic on which the patient was discharged. Clinical interviews, health and psychiatric records and chart reviews were used to collect participants' data. The scale we used in this research in order to assess adherence was Kemp's 7-point scale. Three board-certified psychiatrists used the ROLIN index separately to check inter-rater reliability. The study was approved by the local ethics committee.

Participants

During the 10-year research period, 1,116 different patients with schizophrenia were hospitalized. Out of these, 477 (42.7%) met the age eligibility criteria (18 to 45 years old). A total of 225 patients out of 477 (47.1%) with the mean age of 37.8 years (SD

± 5.9) had never had treatment with LAIs and was included in final statistics.

Rating Opportunity for Long-Acting Injectable Antipsychotic Initiation Index

It is estimated that 50% of patients suffering from chronic illness are not taking medication as prescribed after six months (26). This phenomenon, part of the human nature, is not only present in mental illnesses but also in chronic diseases such as diabetes, hypertension, cerebrovascular diseases (27). The rate of non-adherence with antipsychotics in schizophrenia varies between studies, reflecting differences in the populations studied and the methodology used in terms of the definition and measurement of adherence and the period of time over which it is assessed (11, 28).

According to our experience correlated with the literature on non-adherence topic (11) we proposed index's items derived from the most important elements involved in the outcome of schizophrenia: age, duration of illness, number of relapses, antipsychotic treatment response, family support and adherence.

- Age. The patient's age is a key factor in the subsequent evolution. Young patients may still have many neurocognitive resources needed for treatment response, remission and recovery (29).

Recent studies have shown that patients in the early stages of the disease can more easily accept this type of treatment (30). Thus, for the age of 18 to 25 years we scored 5 points, for the age of 26 to 35 years we scored 3 points, and for those aged between 36 and 45 years, we scored 1 point.

- Duration of illness. Studies show that neuropathological changes occur in the first years of the disease (31). Thus, the first 2–5 years can be considered of major importance for the patient. We rated 5 points for patients with disease duration of 2 to 5 years, 3 points for duration of 6 to 10 years and 1 point for disease duration over 10 years.
- Relapses. Relapses and hospitalizations in the early years are unfavorable prognostic factors; they predict an evolution toward cognitive decline and chronicity (32, 33). Therefore, experts recommend an early initiation of LAI, after the first relapses caused by non-adherence. We rated 5 points for at least 3 relapses, 3 points for 2 relapses and 1 point for 1 relapse.
- Response to oral antipsychotic. Many young people with schizophrenia respond well to the first trials with antipsychotics, a significant percentage even achieve remission (34). Individual responsiveness and the severity of the pathology are criteria that influence the choice of antipsychotic and the doses. The therapeutic response decreases significantly with the increase in the number of relapses (35). 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.
- Family support. Family support is as important as the other elements of therapeutic management (36). 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, presence of a single member was scored 3 points and situations where the patient is alone being scored with 1 point.

- Antipsychotic existing formulation. If the patient received an OAP that also has a LAI formulation (aripiprazole, olanzapine, risperidone, and paliperidone) we scored 5 points, if there was only an oral formulation available (amisulpride and quetiapine) we scored 3 points and if the patient was on clozapine 1 point.
- Treatment adherence. Assessing adherence to treatment is a complex and subjective approach. Many methods have been proposed, none of which is perfect. Generally, the schizophrenia patient can be considered as adherent, partially adherent or non-adherent (13, 37). In the patient's file, upon admission, it is mentioned if the patient is adherent, partially adherent or non-adherent. The adherence was evaluated using

TABLE 2 | Patients characteristics.

Parameters	N = 225
Male gender (n; %)	120; 53.3%
Age (mean, SD)	36.7; $\pm$ 5.6
Age group	
- 18–25 years (n; %)	3; 1.4%
- 26–35 years (n; %)	68; 30.2 %
- 36–45 years (n; %)	154; 68.4 %
Duration of illness (mean, SD)	12.4; $\pm$ 14.1
Duration of illness group	
- 2–5 years (n; %)	51; 22.7 %
- 6–10 years (n; %)	42; 18.6 %
- > 10 years (n; %)	132; 58.7 %
Relapses	
- 2 or more 2 relapses (n; %)	202; 89.8 %
- 1 relapse (n; %)	12; 5.3 %
- No relapse (n; %)	11; 4.9 %
Family support	
- 2 members or more (n; %)	84; 37.3 %
- 1 member (n; %)	92; 40.9 %
- No member (n; %)	49; 21.8 %
Response to oral AP	
- Good response (n; %)	129; 57.3 %
- Partial response (n; %)	93; 41.3 %
- No response (n; %)	3; 1.4 %
Adherence	
- Good (n, %)	31; 13.8 %
- Partial (n, %)	21; 9.3 %
- Non-adherence (n, %)	173; 76.9 %
No of antipsychotics used life time	
- 1 or 2 (n; %)	80; 35.5%
- 3 or 4 (n; %)	95; 42.2%
- 5 or more (n; %)	50; 22.3%

Kemp's 7-point scale (38). For all variants listed, we rated 1 point for good adherence, 3 points for partial adherence and 5 points for poor adherence.

Scoring, Interpretation and Recommendations

All 7 items of the index are of equal importance in the management of the schizophrenia patient when LAI initiation is taken into account. The final score, obtained from summing all 7 individual items scores, could range from a 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, support, and 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 patient category that can benefit from LAI for achieving 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 the patient's autonomy especially in the cases of patients with low support, low income or homeless.

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). The sample size was calculated using G-Power analysis. The normal distribution of value was calculated using Kolmogorov-Smirnov test. Interrater reliability was measured using Cohen's kappa statistics. All statistics were two-tailed.

RESULTS

Patients characteristics of the final sample are presented in **Table 2**.

The total score of the index is calculated by summing the 7 items' scores. There are 15 possible score variants, ranging from 7 to 35. All scores are odd, and some score values appear more frequent than others. In total there are 2,187 (3⁷) variants (**Figure 1**).

The normal distribution of values was assessed with Kolmogorov-Smirnov test (95% CI for the mean = 9.5781 to 20.4219; 95% CI for the median = 6.5920 to 24.8161; *SD* = 9.7907; Coefficient of Skewness = 0.0743;

TABLE 3 | The scale 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 %
Antipsychotic formulation (n; %)	177; 78.7%	43; 19.1%	5; 2.2%
Adherence (n; %)	154; 68.4 %	55; 24.5 %	16; 7.1 %

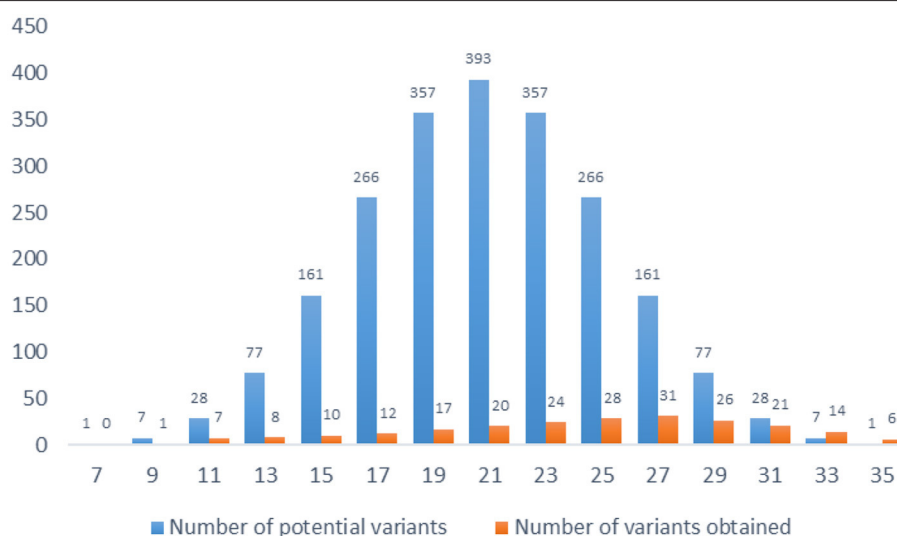


FIGURE 1 | The distribution of ROLIN score.

TABLE 4 | 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.

Coefficient of Kurtosis = -1.1377). The results show a shift to the right because subjects are more likely to get higher results than lower results.

The patients' evaluation with ROLIN showed that 126 patients (56%) had a strong indication for initiating LAI and 88 (39.11%) had a moderate indication. Five patients, discharged on clozapine, without previous long-acting treatment, were considered as having a low indication.

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) (39). A significant number of patients in this age group had a maximum score in at least four items, indicating the need for LAI initiation. Two hundred and three patients (90.2%) had more than 2 relapses. One hundred and five patients (46.7%) lived with at least one family member. Sixty eight percent of patients were non-adherent, which confirms that 2/3 of patients with schizophrenia are not treatment compliant (Table 3).

The results of our research showed that 177 patients (78.7%) were recommended at discharge an OAP that also had a long-acting formulation. A well-known fact in Romania is the clinicians' affinity for olanzapine, an antipsychotic described as being efficient, having low price, and affordable even for the uninsured patients, largely available and having a long-acting formulation. Olanzapine long-acting formulation has the disadvantage of requiring post-injection monitoring for a period of 3 h, which makes it difficult to initiate (a fact that was even more obvious in the current COVID-19 pandemic) (40). The antipsychotics recommended at discharge are presented in Table 4.

The results of our calculations show that our reliability for items assessing ROLIN items is good (Table 5). All 7 items obtained adequate coefficient scores (0.82–1) meaning near perfect agreement.

DISCUSSION

We have described the development and initial standardization of the 7-item index as an instrument for measuring the opportunity for LAI initiation in schizophrenia. As far as we know, this is the first index created to encourage the initiation

TABLE 5 | Interrater reliability for ROLIN items.

ROLIN item	Kappa	Acceptability
Age	1	Adequate
Duration of illness	0.86	Adequate
Relapse	0.92	Adequate
Response to oral antipsychotic	0.82	Adequate
Patient social support	0.96	Adequate
Antipsychotic formulation	1	Adequate
Treatment adherence	0.88	Adequate

ROLIN, rating opportunity for LAI initiation index. All coefficients are within the adequate range (0.82–1.00).

of LAI in schizophrenia, providing evidence and supporting the early initiation of this treatment. Statistical analysis showed a normal distribution of values which is a very important thing that validates the index (skewness = 0.0743; kurtosis = -1.1377).

Although many studies indicate that the use of LAIs may have the potential to prevent relapses and hospitalizations compared to oral antipsychotics (41), and although second-generation LAI formulations are widely available, it has been estimated that only 10–20% of eligible patients are actually prescribed LAIs (42). The results of our research show that a significant number of patients who had an indication for LAI were discharged on 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 we should initiate treatment with these agents. Studies show that initiation is common in severe patients, with involuntary hospitalizations, with evidence of non-adherence to treatment (43). This could lead to a decline in LAI confidence. Fear of more severe side effects may be another explanation, although meta-analyses show that there are no differences between LAIs and OAPs (44). Despite availability of all LAIs formulation in Romania, free of charge for insured patients diagnosed with schizophrenia, a significant percentage of patients with a strong indication for LAIs (64%) were still discharged on OAPs.

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

This index can also enhance the patient's collaboration and the families' engagement in the therapeutic plan, because presenting them the need for initiation score could build a stronger confidence in the clinician's judgment. With minimal time investment, patients and their families could become sufficiently informed in order to accept LAI initiation. It could also help psychiatrists that work only in the outpatient facilities or in private practices to initiate LAI, because this type of treatment is usually initiated in the hospital.

Limitations

Like any instrument, the ROLIN has several limitations. One limitation is the relative small number of cases. Another limitation could be the application of the LAI initiation index to pregnant patients, in which case initiation still raises widespread debate (45) or in the first episode schizophrenia. The present study design did not specifically address effectiveness of the proposed index.

The index must be interpreted with recommendations. In the case of patients with no relapse, there still remains the possibility of therapeutic abandonment, so initiation is a preventive measure. In treatment-resistant schizophrenia, the clinician must assess if it is really a case of treatment resistance or it is rather treatment non-adherence. In the case of a false treatment resistance situation, we recommend LAI initiation. Based on our strong experience in patients on clozapine for

treatment-resistance or for aggressive behavior, a switch to LAI is not recommended. In cases of severe adverse events this switch must be done with caution.

CONCLUSION

The validity of the ROLIN should be upheld by future studies with independent investigators: Its use might be expected to promote uniformity and reliability in research findings.

DATA AVAILABILITY STATEMENT

Data is available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

PI and AT: conception, design of the research, and drafting the manuscript. P-SP: acquisition of data and statistical analysis. PI: analysis and interpretation of data. All authors have read and approved the final manuscript.

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