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REMISSION AND EMPLOYMENT STATUS IN SCHIZOPHRENIA AND OTHER PSYCHOSES: ONE-YEAR PROSPECTIVE STUDY IN CROATIAN PATIENTS TREATED WITH RISPERIDONE LONG ACTING INJECTION

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SUMMARY

Background: *While numerous studies have confirmed the efficacy of risperidone long-acting injectable (RLAI) on many clinical outcomes in patients with schizophrenia, there is no data regarding its influence on employment status.*

Subject and methods: *This was a 12-month observational study with flexible doses of RLAI on a Croatian population of patients with schizophrenia and other psychoses. Visits were at baseline and after 1, 3, 6 and 12 months of treatment. Treatment response was evaluated using Clinical Global Impression of Illness Severity (CGI-S) and Improvement (CGI-I) scales, while remission was defined by 8 items of Positive and Negative Syndrome Scale (PANSS). Employment status was determined at baseline and at study endpoint.*

Results: *A total of 362 patients were included, with a median age of 37 (interquartile range 29-47) years, 63.5 % were males and 67.4% were hospitalised at baseline. Overall 258 (71.3%) patients completed the study. Improvements in CGI-S scores from baseline were significant ($p<0.001$) at all visits. Remission criteria were met in 9 (2.5%) patients at baseline, and in 199 (54.9%) at endpoint, while 144 patients (52.7%) achieved symptomatic remission. Female patients were five times more likely to achieve symptomatic remission (OR=5.2; 95%CI=2.64-10.19). At baseline, 74/362 (20.4%) patients were employed, compared to 77/257 (30.0%) at endpoint ($p<0.001$). Adverse events were spontaneously reported in 55 (15.2%) patients. Three patients died (judged not to be related to RLAI) and one patient committed homicide.*

Conclusions: *Patients treated with RLAI had significant improvements in CGI-S scale scores, hospitalization status, rates of remission and employment status, indicating the benefits of continuous treatment over time. Further studies on the comparative impact of different treatment strategies on functional recovery are needed.*

Key words: *schizophrenia - risperidone long-acting injectable (RLAI) - non-adherence – remission - employment in schizophrenia*

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INTRODUCTION

Schizophrenia is a chronic disabling condition. It requires long-term antipsychotic treatment in order to prevent relapse and achieve stabilization. Relapses occur in the majority of patients, with medication non-adherence being the most important risk factor (Schooler et al. 2003, Emsley et al. 2012). Patients who discontinue antipsychotic medication are almost 5 times more likely to experience relapse (Robinson et al. 1999). The risk of relapse after antipsychotic withdrawal is high even after the first psychotic episode. First-episode patients who discontinued risperidone long-acting injectable (RLAI) had very high relapse rates, with 97% of them having symptom recurrence 36 months after discontinuation (Emsley et al. 2012).

Reduction of severity of psychotic symptoms and relapse prevention has been the aim of treatment of schizophrenia since the introduction of first antipsychotics. Recently, the aims of antipsychotic treatment have moved beyond just behavioural control and relapse prevention, to include the achievement and maintenance of remission (Kane et al. 2008). To define the concept of remission, consensus was reached by the Remission in Schizophrenia Working Group regarding the use of eight items (three positive, three negative and two general symptoms) on the Positive and Negative Syndrome Scale (PANSS) (Andreasen et al. 2005). These items were chosen to represent core symptoms in schizophrenia according to DSM-IV and ICD-10 (Helldin et al. 2006). A further step after achievement of remission is recovery, which has been recently regarded as the new vision for the mental health services (Emsley et al. 2011). While remission is defined using an absolute threshold of the core symptoms of schizophrenia, recovery is a more complex concept, including functional outcome and quality of life (Emsley et al. 2011).

The development of RLAI combines benefits of second generation antipsychotic agent with the adherence advantage of long-acting formulations (Kissling et al. 2005). The efficacy and safety of RLAI in schizophrenia were initially established in a 12-week, double-blind study (Kane et al. 2003), and in two open-label trials, with one-year follow-up (Fleischhacker et al. 2003, Martin et al. 2003). More recent studies reported that treatment with RLAI was also associated with lower rates of future hospitalizations (Schmauss et al. 2007, Peuskens et al. 2010, Lambert et al. 2011, Grimaldi-Bensouda et al. 2012), and improvements in functional status as measured by various scales (Schmauss et al. 2007, Lloyd et al. 2010, Peuskens et al. 2010, Macfadden et al. 2011, Lambert et al. 2011, Bitter et al. 2013, Jakovljevic 2014).

Despite considerable evidence of improvement of functionality with RLAI treatment, we are not aware of any data reporting on its influence on employment status. While remitted patients differed from non-remitters in psychopathological symptoms, health status and medication attitude (Docherty et al. 2007), there is no data investigating the relationship between remission and employment status in patients with schizophrenia. Although employment is the ultimate goal of treatment of schizophrenia, it is rarely achieved. Even patients in remission frequently remain significantly dependent on their caregivers. The only study that we identified investigating the relationship between RLAI and employment was that of Malempati et al. 2011, who reported return to employment in previously disabled patients with bipolar disorder. Given the well-known differences in functional outcomes between bipolar and schizophrenic patients (Möller et al. 2002), those results cannot be generalized to patients with schizophrenia. Therefore it is unknown whether treatment with RLAI, although improving numerous aspects of clinical status, also influences employment status in patients with schizophrenia.

Additionally, there is also evidence that treatment outcomes (Lambert et al. 2010) and healthcare utilization in terms of hospitalizations and duration of hospitalizations (Lambert et al. 2011) during RLAI treatment differ across countries. While numerous studies regarding RLAI treatment in different countries have been published, there is no data regarding RLAI treatment in a Croatian population. The aims of our study were to investigate the rates of remission in Croatian patients treated with RLAI and to determine whether RLAI influences employment status in patients with schizophrenia and related disorders.

SUBJECTS AND METHODS

Subjects

Both, inpatients and outpatients were considered, as long as a change in treatment was indicated. Patients were included irrespective of the reason for the treatment change (e.g. lack of response, side effects, etc.). Eligible patients were aged 18 years or older, met criteria of the diagnostic and statistical manual of mental disorders (4th edition) (DSM-IV) and international classification of diseases (ICD-10) (10th edition) for schizophrenia, schizoaffective disorder or other psychotic disorder, and signed an informed consent document for participation in the study. Patients were enrolled from 16 centres in Croatia, from June, 2007 until February, 2009. Excluded were patients who had a known hypersensitivity to risperidone.

Study design

The investigators informed eligible patients about the study, and invited them to participate. Patients were followed-up through 5 visits. The study design was similar to a previously reported study with RLAI (Kissling et al. 2005). Visits were at the baseline and after 1, 3, 6 and 12 months of treatment. After inclusion, baseline data were collected for demographics, diagnoses, present treatment setting and reasons for switching to RLAI. Illness severity was measured by the Clinical Global Impression-Severity (CGI-S) and CGI-Improvement (CGI-I) scales (Guy 2000). Data for patient employment status were collected at baseline and at endpoint. Remission was defined according to criteria set by Remission in Schizophrenia Working Group, with full symptomatic remission being defined as meeting remission criteria for at least 6 months (Andreasen et al. 2005). We assessed outcome in terms of discontinuation rates, CGI-S and CGI-I changes from baseline and remission rates. We also compared the hospitalization rates and employment status of the patients during the 12 months preceding the study with that of the the 12 month study period. Further, we investigated factors associated with discontinuation, symptom response, hospitalization rates and employment status. Physical examination was performed at baseline. Safety was evaluated by recording adverse events. Due to the naturalistic nature of the study, use of concomitant medication was allowed at the discretion of the investigator. The study was approved by Central Ethics Committee of Croatia and by local Ethics Committees. The study was conducted in accordance with the Declaration of Helsinki and consistent with the principles of Good Clinical Practice.

Data analysis

A level of significance was set to 95% ($p<0.05$), and all confidence intervals were given at the 95% level. In all instances two-tailed tests of statistical significance were used. Wherever the samples were smaller than n=30 exact or Monte Carlo tests of statistical significance were used instead of asymptotic ones. Normality of distribution of continuous variables such as patients age were tested by Kolmogorov-Smirnov test in cases of sub-samples larger than n=30,

and in cases of smaller sub-samples the Shapiro-Wilk test was used. As the measure of central tendencies median and interquartile range were used wherever the distribution significantly deviated from the norm. The association between two independent binary variables such as employment status and gender was accessed by Fisher exact test. In these cases Phi coefficient of association was used as the standardized measure of effect. Differences between two binary, related variables such as employment status at baseline and at the 12th month were analyzed by McNemar test. Changes of CGI-S, and CGI-I were analyzed by Friedman test, and a series of binary outcomes such as achievement of remission criteria at five study points were assessed by Cochran's Q test. All the analyses were carried out using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) statistical software package.

RESULTS

Participants

The study included 362 in and outpatients recruited from 16 centres in Croatia, who required change of their antipsychotic treatment. The majority of patients (n=244, 67.4%) were hospitalized at baseline. Other baseline sample characteristics are summarized in Table 1.

Discontinuations and adverse events

A total of 104/362 (28.7%) dropped out from study. There were no statistically significant differences between those patients who remained in the study and those who discontinued on any of the baseline variables (Table 1).

Main reasons for discontinuing treatment are presented in Table 2.

Table 1. Participants at baseline (n=362) by 12 months of follow up who completed and discontinued RLAI

	All patients (n=362)		Completers (n=258)		Discontinuers (n=104)		P
Age in years (median (IQR)	37	(29-47)	36	(28-46)	38.5	(30-49)	0.159
Males (n (%) of patients)	230	(63.5)	164	(63.6)	66	(63.5)	0.985
Hospitalization at baseline and/or during the 12 months prior to enrolment (n(%) of patients)	299	(83.3)	212	(82.5)	87	(85.3)	0.521
Years since diagnosis (median (IQR)	7	(2-15)	7	(2-15)	6	(2-14)	0.861
Age in years at diagnosis (median (IQR)	26	(22-34)	25	(22-32)	27	(22-35)	0.177
Diagnosis (n (%) of patients)							
Schizophrenia (F20)	233	(64.4)	162	(62.8)	71	(68.3)	0.323
Persistent delusional disorders (F22)	22	(6.1)	16	(6.2)	6	(5.8)	0.886
Acute and transient psychotic disorders (F23)	54	(14.9)	44	(17.1)	10	(9.6)	0.071
Schizoaffective disorders (F25)	35	(9.7)	23	(8.9)	12	(11.5)	0.445
Other*	18	(5.0)	13	(5.0)	5	(4.8)	0.937
Total	362	(100.0)	258	(100.0)	104	(100.0)	
CGI-S (mean (standard deviation)	5.0	(1.1)	5.0	(1.0)	5.1	(1.0)	0.271
Remission (n (%) of patients)	9	(2.5)	5	(1.9)	4	(3.8)	0.291
Reason for initiating RLAI (n(%) of patients)**							
Non-adherence	275	(76.0)	194	(75.2)	81	(77.9)	0.588
Insufficient response	173	(47.8)	127	(49.2)	46	(44.2)	0.389
Unacceptable tolerability/adverse events	66	(18.2)	49	(19.0)	17	(16.3)	0.555
Medication utilization prior to RLAI (n (%) of patients)							
Oral atypical antipsychotics	189	(52.2)	132	(51.2)	57	(54.8)	0.506
Oral conventional	61	(16.9)	46	(17.8)	15	(14.4)	0.254
Oral atypical + oral conventional	74	(20.4)	52	(20.2)	22	(21.2)	0.768
Conventional depot	14	(3.9)	11	(4.3)	3	(2.9)	0.321
Oral atypical + conventional depot	5	(1.4)	4	(1.6)	1	(1.0)	0.479
Oral conventional + conventional depot	8	(2.2)	6	(2.3)	2	(1.9)	0.711
No antipsychotic therapy	11	(3.0)	7	(2.7)	4	(3.8)	0.412
Total	362	(100)	258	(100)	104	(100)	
Employment at baseline (n(%) of patients)							
Employed	74	(20.4)	55	(21.3)	19	(18.3)	0.522
Unemployed or student	217	(59.9)	159	(61.6)	58	(55.8)	0.309
Retired	71	(19.6)	44	(17.1)	27	(26.0)	0.055
Total	362	(100)	258	(100)	104	(100)	

Abbreviations: IQR = interquartile range; CGI = Clinical Global Impression scale; RLAI = risperidone long-acting injection; P = level of statistical significance, or probability of type I (alpha)

* Other includes: Schizotypal disorder (F21) 6 (1.7%); Unspecified nonorganic psychosis (F29) 12 (3.4%)

** Some patients had two or three reasons for switching.

Table 2. Reasons for discontinuation

	n	(%)
Lost to follow up	47	(45.6)
Non-adherence	22	(21.4)
Adverse events	12	(11.7)
Insufficient response	9	(8.7)
Death of patients	3	(2.9)
Other	11	(10.6)
Total	103*	(100.0)

Reason for discontinuation was not properly collected for 1/104 (1.0%) patient

Table 3. Mean RLAI dosages

	n	mean	(SD)
Baseline	362	34.3	(8.05)
1st month	344	35.9	(7.88)
3rd month	321	36.8	(8.09)
6th month	292	37.0	(8.21)
12th month	258	37.3	(8.36)

Table 4. Achievement of remission after 12 months of RLAI treatment (n=274)

N (%)	Achieving remission		Not achieving remission		Total		OR (95% CI)	
All patients	199	(72.6)	75	(27.4)	274	(100)		
Age (median; IQR)	35	(27-46)	40	(33-48)			1.0	(0.92-1.03)
Gender								
male	116	(68.2)	54	(31.8)	170	(100)	1	
female	83	(79.8)	21	(20.2)	104	(100)	4.1	(1.50-11.02)*
Hospitalization at baseline or during the 12 months prior to enrolment								
outpatients	32	(64.0)	18	(36.0)	50	(100)	1	
hospitalized	166	(74.8)	56	(25.2)	222	(100)	1.3	(0.42-3.90)
Years since diagnosis (median, IQR)	5	(1-13)	7	(2-17)			1.0	(0.92-1.06)
Age at diagnosis (median, IQR)	25	(21-33)	27	(23-32)			1.0	(0.95-1.01)
Diagnosis								
schizophrenia (F20)	116	(67.1)	57	(32.9)	173	(100)	1	
acute and transient psych. disorders (F23)	40	(88.9)	5	(11.1)	45	(100)	0.8	(0.13-4.62)
schizoaffective disorders (F25)	20	(80.0)	5	(20.0)	25	(100)	1.1	(0.13-8.79)
persistent delusional disorders (F22)	14	(82.4)	3	(17.6)	17	(100)	0.6	(0.06-6.09)
other*	9	(64.3)	5	(35.7)	14	(100)	0.5	(0.03-7.22)
CGI-S at baseline (median, IQR)	2	(2-3)	4	(3-5)			0.17	(0.10-0.29)*
Atypical antipsychotics prior to RLAI								
no	52	(70.3)	22	(29.7)	74	(100)	1	
yes	147	(73.5)	53	(26.5)	200	(100)	0.8	(0.24-2.54)
Conventional antipsychotics prior to RLAI								
no	117	(79.1)	31	(20.9)	148	(100)	1	
yes	82	(65.1)	44	(34.9)	126	(100)	0.5	(0.20-1.43)
Reason for initiating RLAI								
Unacceptable tolerability/adverse events								
no	160	(72.1)	62	(27.9)	222	(100)	1	
yes	39	(75.0)	13	(25.0)	52	(100)	1.1	(0.32-3.67)
Adherence								
no	46	(67.6)	22	(32.4)	68	(100)	1	
yes	153	(74.3)	53	(25.7)	206	(100)	0.6	(0.17-1.86)
Insufficient response								
no	102	(74.5)	35	(25.5)	137	(100)	1	
yes	97	(70.8)	40	(29.2)	137	(100)	1.8	(0.66-4.61)

Abbrevations: OR=adjusted odds ratio (multivariate logistic analysis); 95%CI= odds ratio 95% confidence intervals; IQR = Interquartile range; * Variables statistically significantly (at $p \leq 0.05$) associated with symptomatic remission;
* Other includes: Schizotypal disorder (F21); Unspecified nonorganic psychosis (F29); Bipolar affective disorder (F31); Depressive episode (F32)

Out of all patients (both discontinuers and those who remained in the study) adverse events were reported in 55 (15.2%) of patients, with the most frequent being hospitalization (n=31, 8.6%), death (n=3, 0.8%) (causes of death were: pulmonary embolism, freezing and unknown cause), galactorrhoea (n=3, 0.8%), amenorrhoea (n=3, 0.8%), restlessness n=3, 0.8%), weight gain (n=2, 0.6%), EPD (n=2, 0.6%), psychomotor slowing with muscular rigidity (n=2, 0.6%) and all other adverse events in 1 (0.3%) of patients, respectively. One patient committed homicide.

RLAI dose

Mean RLAI dose at each visit is presented in Table 3.

Friedman test indicated that the average RLAI dosage significantly increased during the study (n=257; χ^2=121.3; df=4; p<0.001).

Hospitalizations

At baseline 244/362 (67.4%) patients were hospitalized. During the 12 months of the study 31/362 (8.6%) patients were hospitalized. Significantly fewer patients were hospitalized during the 12 month study period (n=31/362) (8.6%), than in the 12 months preceding the study entry (n=299/359) (83.3%) (missing data for 3 patients). Change in number of hospitalized patients was statistically significant (McNemar test, n=359, χ^2=258.3; p<0.001).

Positive change was defined as: no new hospitalizations during the study among the patients that were hospitalized at the inclusion or during the 12 months before the study. There were 272/359 (75.8%), (95%CI=71.4-80.2%) such patients. After adjusting for gender, age, duration of illness, diagnosis, and previous therapy, positive change was statistically significantly associated previous non-adherence as the reason for switching to RLAI. Those patients had almost six times higher odds (OR=5.8; 95%CI=2.9-11.8%) for the positive change compared to patients who switched to RLAI due to reasons other than non-adherence.

After adjusting for age, gender, duration of illness, age at first diagnosis, baseline CGI-S, diagnosis, and previous therapy, non-adherence was significantly associated with insufficient response to previous treatment (OR=0.08; 95%CI=0.04-0.17).

Table 5. Achievement of symptomatic remission after 12 months of RLAI treatment (n=273)

N (%)	Achieving remission		Not achieving remission		Total		OR (95% CI)	
All patients	144	(52.7)	129	(47.3)	273	(100)		
Age (median; IQR)	36	(28-48)	38	(29-46)	37	(28-46)	1.1	(0.41-2.78)
Gender								
male	72	(42.6)	97	(57.4)	169	(100)	1	
female	72	(69.2)	32	(30.8)	104	(100)	5.2	(2.64-10.19)*
Hospitalization at baseline or during the 12 months prior to enrolment								
outpatients	22	(44.0)	28	(56.0)	50	(100)	1	
hospitalized	121	(54.8)	100	(45.2)	221	(100)	2.2	(0.99-5.01)
Years since diagnosis (median, IQR)	5	(1-15)	7	(2-15)	6	(1-15)	1.0	(0.93-1.09)
Age at diagnosis (median, IQR)	26	(21-34)	25	(22-32)	26	(22-33)	1.0	(0.90-1.05)
Diagnosis								
schizophrenia (F20)	76	(44.2)	96	(55.8)	172	(100)	1	
acute and transient psych. disorders (F23)	34	(75.6)	11	(24.4)	45	(100)	4.5	(1.86-10.74)*
schizoaffective disorders (F25)	17	(68.0)	8	(32.0)	25	(100)	2.2	(0.78-6.47)
persistent delusional disorders (F22)	10	(58.8)	7	(41.2)	17	(100)	2.3	(0.66-8.32)
other*	7	(50.0)	7	(50.0)	14	(100)	2.5	(0.46-13.86)
CGI-S at baseline (median, IQR)	5	(4-5)	5	(4-6)	5	(4-6)	0.93	(0.27-3.19)
Atypical antipsychotics prior to RLAI								
no	40	(54.8)	33	(45.2)	73	(100)	1	
yes	104	(52.0)	96	(48.0)	200	(100)	0.87	(0.39-1.97)
Conventional antipsychotics prior to RLAI								
no	80	(54.1)	68	(45.9)	148	(100)	1	
yes	64	(51.2)	61	(48.8)	125	(100)	1.1	(0.55-2.16)
Reason for initiating RLAI								
Unacceptable tolerability/adverse events								
no	113	(51.1)	108	(48.9)	221	(100)	1	
yes	31	(59.6)	21	(40.4)	52	(100)	1.5	(0.68-3.20)
Adherence								
no	34	(50.0)	34	(50.0)	68	(100)	1	
yes	110	(53.7)	95	(46.3)	205	(100)	0.7	(0.33-1.65)
Insufficient response								
no	79	(58.1)	57	(41.9)	136	(100)	1	
yes	65	(47.4)	72	(52.6)	137	(100)	0.60	(0.31-1.15)

Abbrevations: OR=adjusted odds ratio (multivariate logistic analysis); 95%CI= odds ratio 95% confidence intervals; IQR = Interquartile range; * Variables statistically significantly (at p≤0.05) associated with symptomatic remission;
* Other includes: Schizotypal disorder (F21); Unspecified nonorganic psychosis (F29); Bipolar affective disorder (F31); Depressive episode (F32)

Symptom improvement

There was statistically significant decrease in CGI – S score (Friedman test; n=257, χ^2=753.7; p<0.001). Median CGI – S decreased from 5.0 at baseline to 2.8 after 12 months and in the CGI – I score (Friedman test; n=257, χ^2=243.5; p<0.001). Median (interquartile range) CGI – I decreased from 2 (2-3) at baseline down to 2 (2-2) at 12 months.

Remission

A statistically significant increase in the number of patients who achieved remission was observed (Cochran's test; n=273, Q=473.9; df=4; p<0.001). While at baseline only 9/362 (2.5%) of patients were in remission, after 12 months of RLAI treatment, 199/274 (72.6%) patients achieved remission. In addition, 144/273 patients (52.7%; 95%CI=46.7-58.6%) achieved symptomatic remission at the end of the study (Tables 4 and 5).

After adjustment for age, duration of illness, diagnosis, previous therapy, CGI-S at baseline, and the reason for the change of therapy to RLAI, gender, and diagnosis of acute and transient psychotic disorder were associated with the achievement of symptomatic remission. Female patients had five times higher likelihood (OR=5.2; 95%CI=2.64-10.19%) of achieving symptomatic remission than male patients. This difference was statistically significant (Fisher Exact test, φ=0.26, p<0.001). Patients diagnosed with acute and transient psychotic disorder had over four times higher odds (OR=4.5; 95%CI=1.86-10.74%) of achieving symptomatic remission compared to those diagnosed with schizophrenia.

Employment

In the analysis of employment we omitted the patients who were receiving disability pension at baseline, 71/362 (19.6%), because their employment status could not have changed. Of remaining patients, 74/291 (25.4%; 95%CI=20.4-30.3%) were employed at the baseline. After 12 months of RLAI treatment, 77/205 (37.6%; 95%CI=31.0-44.2%) of patients were employed. Data were not collected for 105/362 (29.0%) of patients who were lost to follow up. The change in the number of employed patients was statistically significant (McNemar test, n=205, χ^2=18.4; p<0.001). Of the patients that were unemployed at the baseline, 30/142 (21.1%; 95%CI=14.4-27.8%) had obtained employment at the end of the study (Table 6).

Age at baseline was significantly correlated with change in employment status after the 12 of RLAI treatment (Mann-Whitney test, U=1192, Z=-2.4; p=0.012; Eta (with change in employment as the dependent variable) =0.52). Patients who experienced a positive change (i.e. those who were unemployed at the baseline, and found employment during the study) were significantly younger (median (interquartile range) = (28.5 (24.8-39.3) years), than the patients who remained unemployed (35 (27.3-44.8) years). We did not find any significant differences in the positive change in employment status between men and women, nor across different diagnostic categories. We further analyzed the relation between employment statuses in patients who achieved symptomatic remission, compared to those who did not achieve it (Table 7).

Differences in baseline employment status between the patients who did and did not achieve symptomatic remission 12 months of RLAI were not statistically significant (Fisher Exact test, p=0.169). Among those who achieved symptomatic remission, 52/117 (44.4%) were employed at the study endpoint, compared to 25/88 (28.4%) among those who did not achieve symptomatic remission. The increase in the number of employed patients was statistically significant among those who achieved symptomatic remission (McNemar test, p<0.001), and among those who failed to achieve symptomatic remission (McNemar test, p=0.039).

Table 6. Difference in number of employed patients at the baseline and after 12 months therapy with RLAI (n=205)

N (%)	Employed after 12 months		Not employed after 12 months		Total		χ^2	P
Employed at baseline	47	(92.2)	4	(7.8)	51	(100)	18.4	<0.001
Not employed before	30	(19.5)	124	(80.5)	154	(100)		

Abbreviations: χ^2 = McNemar test Chi square statistic; P = level of statistical significance

Table 7. Relationship between employment status and achievement of symptomatic remisson (n=205; omitted: n=52 receiving disability pension, n=105 lost to follow up)

N/total (%)	Employed				P
	At baseline		After 12 months		
Symptomatic remission					
achieved	36/124	(29.0)	52/117	(44.4)	<0.001
not achieved	21/101	(20.8)	25/88	(28.4)	0.065

Abbreviations: P = McNemar test; level of statistical significance

DISCUSSION

This Croatian observational study provides further supportive evidence for the effectiveness of RLAI in terms of decreasing overall severity of psychotic symptoms (Lloyd et al. 2010, Parellada et al. 2010, Lambert et al. 2011, Macfadden et al. 2011, Dubois et al. 2014) and achieving remission in a subgroup of patients (Kissling et al. 2005, Llorca et al. 2008, Rossi et al. 2009, Lambert et al. 2010). Our sample was characterized by very low rates of remission at baseline. This could be attributed to poor adherence of patients to their current antipsychotic regimen, consistent with the fact that the majority (67.4%) of patients were initially hospitalized and had a mean baseline CGI-S score of 5.0±1.1. Our study differs from other RLAI studies that included mostly stable patients (Kissling et al. 2005, Lasser et al. 2005, Llorca et al. 2008, Rossi et al. 2009, Lambert et al. 2010, Lloyd et al. 2010) who were almost twice less likely than our patients to be hospitalized at baseline (Grimaldi et al. 2012). The likely reason for including a larger number of clinically unstable patients in the present study is that RLAI prescription guidelines in Croatia restrict its use to patients who experience worsening of psychosis and are non-adherent to medication.

In our study the rates of remission increased from 2.34% at baseline to 72.6% in the patients who completed 12-month treatment with RLAI. These results are in agreement with other studies. In the StoRMI study, 44.8% of patients who were not initially in remission, achieved remission after 18 months of RLAI treatment (Llorca et al. 2008). In the study of first-episode patients, 64% patients achieved remission during 24-month RLAI treatment (Emsley et al. 2008). In another study the proportion of patients who meet remission criteria increased from 29% at baseline to 60% at endpoint (Kissling et al. 2005). The one-year completion rate in our study was 71.3%, which is also similar to other studies. Completion rates with RLAI treatment were 84% after 6 months (Parellada et al. 2010); between 57.3% (Macffadden et al. 2011), 65% (Fleischacker et al. 2003), and 70% (Rossi et al. 2009) after 12 months; between 39.9% (Lambert et al. 2010) and 44.3% after 18 months (Llorca et al. 2008) and from 39.3% (Macfadden et al. 2011) to even 85% (Peuskens et al. 2010) after 24 months of RLAI treatment, respectively. Together these results suggest that remission is a realistic treatment target in schizophrenia and can be anticipated in a substantial number of patients who remain adherent to treatment over time (Emsley et al. 2011).

The high remission rate observed in our study may be related to good adherence achieved with RLAI therapy (Kissling et al. 2005) as adherent patients are less likely to relapse compared to those who are poorly compliant (Thieda et al. 2003, Gilmer et al. 2004). Our patients who started RLAI treatment due to non-adherence to previous treatment had an almost six-fold reduced chance of being hospitalized in next 12 months, compared to patients who switched to RLAI due to other reasons. This finding is also in line with other studies that reported that patients treated with RLAI had significant reductions in duration of hospitalization (Turner & Urquhart 2004), which in turn was also associated with lower overall treatment costs.

In our study only 2 patients had clinically significant weight gain, which is in line with another study reporting no weight gain during RLAI treatment (Rossi et al. 2009). These findings are important because patients with schizophrenia are at high risk for metabolic syndrome. Treatment with RLAI was overall well-tolerated in our patients, with only 15.2% reporting adverse events. Because of the naturalistic nature of study it is likely that all adverse events may not have been reported. Nevertheless, our findings are consistent with other studies reporting good tolerability with RLAI (Chue et al. 2003, Fleischhacker et al. 2003, Kane et al. 2003, Jovanovic et al. 2010, Doknic et al. 2011).

In our sample females had five times higher odds of achieving symptomatic remission at endpoint compared to males. Gender differences in response to antipsychotics have been reported previously. Female gender was a predictor of functional remission after one year of treatment with different antipsychotics (Spellmann et al. 2012) and of less severe negative symptoms in first-episode patients (Simonsen et al. 2007). In first-episode patients treated with RLAI, chance of remission was increased in women (Emsley et al. 2008). On the other hand, male gender predicted relapse in patients treated with RLAI (Lambert et al. 2010), which could not be attributed to pharmacokinetic issues (Aichorn et al. 2005). However, in another study no gender differences were observed in response to risperidone, although in the same study women responded better to clozapine (Usall et al. 2007). These studies, together with our findings, suggest that women with schizophrenia tend to have more favorable responses to antipsychotic treatment. Biological factors, such as sex steroid hormones, as well as psychosocial influences may play a role in these gender differences in response to antipsychotics (Mendrek & Stip 2011).

While the initial RLAI dose in our study was 25 or 37.5 mg every two weeks, the mean dose at month 3 of treatment was 36.02 (±9.62) mg every two weeks. This suggests that initiation doses may not have been fully effective and is consistent with the suggestion that a dose of 25 mg RLAI every two weeks is associated with a greater probability of treatment discontinuation (Taylor et al. 2009). Our findings support the use of RLAI in patients with schizophrenia and other psychoses. However, despite the fact that at least one-third of patients with schizophrenia are non-adherent to their prescribed medication regimen (West et al. 2005), the use of long-acting preparations in non-adherent schizophrenic populations is still uncommon (West et al. 2008).

One of the most important goals in the treatment of patients with schizophrenia is to achieve functional recovery. Our patients achieved high rates of symptomatic remission, and a subgroup also had positive change in their employment status. This is not unexpected, as impairment of functioning has been associated with lower remission rates (Haro et al. 2011). Both long-term antipsychotic treatment and psychosocial rehabilitation are important treatment components in schizophrenia, with re-establishment of employment emerging as an ultimate goal. This would certainly be the case for our sample who, with a mean age of 38 years, were in their most productive age.

This study has several limitations: The study was open label and non-comparative. Also, adherence to previous antipsychotic treatment was not measured; no specific scales to assess functioning were administered; and only full time, formal employment was taken as the employment status indicator. Accordingly, we may have introduced a bias and jeopardized internal validity of the outcome variable as we had not collected data on part time jobs, and employment within the informal economic segment.

CONCLUSIONS

Our study provides further evidence to suggest that switching to RLAI in purely naturalistic conditions can help patients to achieve remission. Treatment with RLAI was safe and well-tolerated. To the best of our knowledge, this is the first RLAI study to investigate the employment status in patients with schizophrenia and related psychoses. We found that RLAI treatment might improve the employment rate in previously unemployed patients. Although remission in schizophrenia is considered an important step towards functional recovery, its relationship with employment status is still under investigated.

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Conflict of interest:

Drs. A. Mihaljevic Peles, Sagud and Grosic have received honoraria from: Abbott, AstraZeneca, Eli Lilly, Janssen, Pfizer, Servier, Lundbeck. Drs. I. Simunovic Filipcic and I. Pedisic were Janssen employees. Dr. R. Emsley has participated in speakers/advisory boards and received honoraria from AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, Lundbeck, and Servier. He has received research funding from Janssen, Lundbeck and AstraZeneca.

Contribution of individual authors:

Alma Mihaljevic Peles was involved with study design, data collection, data interpretation and manuscript preparation. *Marina Sagud* was involved with study design, data collection, data interpretation and manuscript preparation. *Ivona Simunovic Filipcic & Ivana Pedisic* were involved with study design, data interpretation and manuscript preparation. *Vladimir Grosic* was involved in data collection and manuscript preparation. *Robin Emsley* reviewed draft manuscript.

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