

ORAL VERSUS LONG-ACTING INJECTABLE ANTIPSYCHOTICS: HOSPITALISATION RATE OF PSYCHOTIC PATIENTS DISCHARGED FROM AN ITALIAN PSYCHIATRIC UNIT

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SUMMARY

Objective: The primary aim is to verify the efficacy of long-acting injectable (LAI) and oral antipsychotics (AP) in terms of re-hospitalisation rate of patients with psychotic disorders. The second aim is to evaluate socio-demographic and clinical differences in patients that were re-hospitalised after the index discharge compared to patients that were not re-hospitalised. Finally, socio-demographic and clinical differences of re-hospitalised patients that were prescribed at discharge with oral or LAI AP were analysed.

Methods: A retrospective observational study including all patients discharged with diagnosis of psychotic disorders from July 2011 to July 2013 was conducted. Patients discharged with LAI or with oral AP were included. Re-hospitalisations occurred during a follow-up period of 24 months after the index discharge were considered. Chi-square test or Student's t-test were used for comparisons. Odds ratios (OR) and 95% confidence intervals (CI) for the incidence of re-hospitalisation for LAI or oral AP were provided.

Results: No significant differences between LAI and oral AP in terms of re-hospitalisation rate in a 24-month period were found. Clinical and socio-demographic characteristics did not significantly differ between the groups.

Conclusions: LAI seemed to be similar to oral AP in terms of prevention of re-hospitalisation in psychotic patients.

Key words: long-acting injectable antipsychotic - oral antipsychotic - psychosis - hospitalisation rate - relapse prevention

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INTRODUCTION

Schizophrenia is a severe psychiatric disorder characterized by positive symptoms, negative symptoms and cognitive impairment (Owen 2016). International epidemiological studies indicate an incidence ranging from 0.11 to 0.69 per 1000 inhabitants, whilst the prevalence was estimated between 0.6 and 0.8% (McGrath 2008).

In Italy, with an adult population (≥ 18 years) of about 49 million individuals, it can be estimated that there are about 245,000 people affected by schizophrenia or who suffered from a schizophrenic disorder in some period in their life (De Masi 2007).

Psychopharmacological therapy is the focus of the treatment of schizophrenia, leading to substantial improvements in psychosocial interventions (Mueser & McGurk 2004).

Although clinical studies have shown that antipsychotic medication can reduce up to 30-40% the frequency of recurrences of psychotic disorders (Davis 1994), the rate of psychotic patients who are partially or completely non-adherent to the treatment with oral antipsychotics (AP) varies between 40 and 60% (Olivares 2011). Furthermore, there are no real differences observed between first and second generation oral AP as for efficacy (Crossley 2010, Velligan 2009). Non-compliance is an important risk factor for schizophrenia recurrence (Haddad 2014, Leucht & Heres 2006) which can be evaluated in terms of re-hospitalisation (Weiden 2004).

The main advantage of long-acting injectable antipsychotics (LAI) is to ensure stable plasma levels of the active medication, thus overcoming the problems associated with non-adherence to drug treatment (De Risio & Lang 2014). As a consequence, it is reasonable to think that the injectable formulations are responsible for the prevention of recurrence related to non-compliance (De Risio & Lang 2014).

On the bases of recent literature, evidence in favor of the superiority of LAI over oral AP in terms of recurrence prevention appears to be ambivalent and dependent on the design of the trial (Montemagni 2016). In fact, few studies report a significantly lower risk of re-hospitalisation for patients prescribed with LAI instead of the oral formulation (Tijoren 2011, Suzuki 2016, Leucht 2011, Kishimoto 2014). On the other hand, other studies showed no statistically significant difference between LAI and oral AP in preventing recurrence and re-hospitalisation (Fusar-Poli 2013, Kishimoto 2013, Buckley 2015).

It is for these reasons that we developed this retrospective observational cohort study with the primary aim to verify the efficacy of LAI and oral AP in preventing re-hospitalisations of patients suffering from psychotic disorders. The second aim was to evaluate socio-demographic and clinical differences in patients that were re-hospitalised after the index discharge compared to patients that were not re-hospitalised. Finally, socio-demographic and clinical differences of re-hospitalised patients that were prescribed at discharge with LAI or oral AP were analysed.

METHODS

Procedures

The medical records of all the patients discharged from the Psychiatric Inpatient Unit of the "Santa Maria della Misericordia" Hospital in Perugia were analysed. The records of the patients discharged with AP and diagnosed with "Schizophrenia Spectrum and Other Psychotic Disorders" according to DSM-5 from 1 July 2011 to 1 July 2013 were selected. The index discharge has been designated as the first discharge occurred in a period of two years. For each patient we considered the number and characteristics of the re-hospitalisations occurred during a 24-month period of follow-up from the index discharge.

Criteria for inclusion and exclusion

All the patients aged 18 or older and diagnosed with a "Schizophrenia Spectrum and Other Psychotic Disorders" and discharged with AP therapy have been included in the study.

The patients transferred to the psychiatric wards of other cities immediately after admission for territorial competency or subsequently transferred to our hospital for the same reason were excluded.

Sample

From July, 1 2011 to July, 1 2013, 833 patients have been hospitalised at the Inpatient Psychiatric Unit of the "Santa Maria della Misericordia" Hospital in Perugia. Between them, 816 patients were diagnosed with a DSM-5 "Schizophrenia Spectrum and Other Psychotic Disorders" and treated with AP. Patients discharged with LAI (n=161) and with oral AP (n=655) were selected. Repeated hospitalisations have been excluded. The final sample was composed of 213 patients, 67 discharged with a LAI AP and 146 with oral AP.

Statistical analysis

The statistical analysis proceeded according to the following steps:

- Descriptive statistical analysis for demographic and clinical characteristics of the sample.
- Bivariate Analysis. The Chi-square test was used to compare patients re-hospitalised following the index discharge with patients without further admission. Continuous variables were evaluated using the Kolmogorov-Smirnov test to evaluate the normality of distribution. The student T test was used to assess the differences between the distributions of continuous variables between the groups with or without re-hospitalisation following the index discharge. Similarly, patients discharged with oral AP versus LAI re-hospitalised during the follow-up have been compared.

- Hospitalisation rates, odds ratios (OR) and 95% confidence intervals for the incidence of re-hospitalisations during the follow-up period for patients prescribed with LAI versus oral AP, typical versus atypical AP, have been proposed.

All *p* values were two-tailed and statistical significance was set at $p < 0.05$. The statistical analysis was performed using the SPSS version 23.0.0 software (Statistical Package for Social Sciences-SPSS, version 23.0.0 for Windows Inc., Chicago, IL, USA).

Table 1. Socio-demographic characteristics of the sample (n=213)

	n (%)
Sex	
Male	110 (51.6)
Female	103 (48.4)
Marital status	
Single	141 (66.2)
Married	48 (22.5)
Divorced/Widow/Not declared	24 (11.3)
Nationality	
Italian	171 (80.3)
Foreign	42 (19.7)
Already in treatment at a Mental Health Center	
Yes	144 (67.6)
No	69 (32.4)
Type of hospitalization	
Involuntary	102 (47.9)
Voluntary	111 (52.1)
Already in treatment when hospitalized	
Yes	137 (64.3)
No	76 (35.7)
Reason for hospitalization	
Thought disorders/psychotic symptoms	114 (53.5%)
Impulsivity/Impulse control disorder/Behavioral disorders	58 (27.2%)
Eating disorders	17 (8.0%)
Suicide attempt/Suicidal ideation/ Self-injurious behaviours	13 (6.1%)
Mood disorders/Anxiety/ Obsessive thinking	11 (5.2%)
	M (SD)
Age (years)	42.41 (13.63)
Length of stay (index hospitalization) (days)	14.78 (11.37)

n = number; M = mean; SD = standard deviation

RESULTS

Socio-demographic characteristics of the sample

The study population was composed of 213 patients with an average age of 42.41 ± 13.63 years. Most of the study participants were single (66.2%), a quarter of them (22.5%) were married and a minority (11.3%) declared to be separated/divorced/widowed or did not declare any status. Most of the patients were Italian (80.3%) and have been hospitalised following a request

of the mental health service (67.6%), and generally it was voluntary the hospitalisation (52.1%). The majority of the sample (64.3%) was already in treatment at the local mental health service. The most frequent reason for hospitalisation (53.5%) was the presence of thought disorders or psychotic features (see table 1). Around a fifth of the patients (21.6%) presented a medical comorbidity. Patients were generally discharged at home with the care of the local mental health service (68.5%).

Table 2. Antipsychotic treatment at index discharge (n=213)

	n (%)
LAI	67 (34.3)
Typical	48 (22.5)
Atypical	19 (8.9)
Oral AP	146 (68.5)
Typical	49 (23.0)
Atypical	73 (34.3)
Typical and atypical	24 (11.3)

AP = antipsychotic; n = number;
 LAI = long acting injectable antipsychotic

The average length of stay of the index hospitalisation was 14.78±11.37 days. At the index discharge, 68.5% of the patients (n=146) were prescribed with oral AP whilst 34.3% (n=67) with a LAI (see table 2). As for the oral formulation, second generation AP were generally the most prescribed (34.3%), whilst typical AP was most frequently prescribed in the LAI formulation (22.5%).

Re-hospitalisation after the index discharge

During the 24-month follow-up, 73 out of 213 patients (34.3%) of the sample had a recurrence that required a new hospitalisation. The patients that were re-hospitalised (see table 3) were predominantly male (60.3%), Italians (79.5%), single (68.5%), with an average age of 40.73±12.73 years, slightly lower than the average age of the not re-hospitalised patients (43.29±14.04 years).

The differences in gender, nationality, marital status and age between the two groups were not statistically significant.

Table 3. Re-hospitalization within 24 months (n=213)

	Yes n (%)	No n (%)	χ^2	P
Sex				
Male	44 (60.3)	66 (47.1)	2.808	0.094
Marital status				
Single	50 (68.5)	91 (65.0)	0.129	0.720
Married	16 (21.9)	32 (22.9)	0.000	1.000
Divorced/Widow/Not declared	7 (9.6)	17 (12.1)	0.110	0.741
Nationality				
Italian	58 (79.5)	113 (80.7)	0.001	0.969
Already in treatment at a Mental Health Service				
Yes	53 (72.6)	91 (65.0)	0.943	0.332
Type of hospitalisation				
Voluntary	39 (53.4)	72 (51.4)	0.017	0.895
Reason for hospitalization				
Mood disorders/Anxiety/Obsessive thinking	2 (2.7)	9 (6.4)	0.686	0.407
Thought disorders/psychotic symptoms	35 (47.9)	79 (56.4)	1.068	0.301
Impulsivity/Impulse control disorder/Behavioral disorders	24 (32.9)	34 (24.3)	1.380	0.240
Suicide attempt/Suicidal ideation/Self-injurious behaviours	5 (6.8)	8 (5.7)	0.001	0.979
Eating disorders	4 (5.5)	8 (5.7)	0.000	1.000
Comorbid medical disorder				
No	61 (83.6)	106 (75.7)	1.312	0.252
Type of discharge				
Home+mental health service	55 (75.3)	102 (72.9)	0.052	0.820
Residency/Prison	13 (17.8)	26 (18.6)	0.000	1.000
Other psychiatric ward (different city)	5 (6.8)	12 (8.6)	0.030	0.862
Already taking medication (before the index hospitalization)				
Yes	47 (64.4)	90 (64.3)	0.000	1.000
	M (SD)	M (SD)	T	p=0.05
Age	40.73 (12.733)	43.29 (14.035)	1.307	0.193
Length of stay	15.08 (10.847)	14.63 (11.668)	-0.276	0.783

n = number; M = mean; SD = standard deviation; χ^2 = Chi-square test; T = Student's t-test

Table 4. Re-hospitalisation during the 24-month follow-up and type of AP treatment (n=213)

	Yes n (%)	No n (%)	χ^2	p=0.05
Oral AP	46 (63.0)	100 (71.4)	1.210	0.271
LAI	27 (37.0)	40 (28.6)	1.210	0.271

AP = antipsychotic; n = number; LAI = long acting injectable antipsychotic; χ^2 = Chi-square test

Table 5. Rates of re-hospitalisation (n=213)

	Yes n (%)	No n (%)	χ^2	p=0.05	OR	IC 95%
LAI						
Typical	19 (26.0)	29 (20.7)	0.501	0.479	1.347	0.694-2.615
Atypical	8 (11.0)	11 (7.9)	0.251	0.617	1.443	0.554-3.763
Oral AP						
Typical	12 (16.4)	37 (26.4)	2.169	0.141	0.548	0.265-1.130
Atypical	25 (34.2)	48 (34.3)	0.000	1.000	0.998	0.550-1.812
Typical and atypical	9 (12.3)	15 (10.7)	0.016	0.900	1.172	0.486-2.824

AP = antipsychotic; IC = confidence intervals; n = number; χ^2 = Chi-square test; T = Student's t-test;
 LAI = long acting injectable antipsychotic, OR = Odds Ratio;

Table 6. Re-hospitalisation during the 24-month follow-up, type of AP treatment, socio-demographic and clinical characteristics (n=213)

	Yes n (%)	No n (%)	χ^2	P
Sex				
Male	28 (60.9)	16 (59.3)	0.000	1.000
Marital status				
Single	31 (67.4)	19 (70.4)	0.000	0.997
Married	10 (21.7)	6 (22.2)	0.000	1.000
Divorced/Widow/Not declared	5 (10.9)	2 (7.4)	0.005	0.942
Nationality				
Italian	39 (84.8)	19 (70.4)	1.372	0.241
Already in treatment at a Mental Health Service				
Yes	32 (69.6)	21 (77.8)	0.238	0.626
Type of hospitalisation				
Voluntary	20 (43.5)	14 (51.9)	0.202	0.653
Reason for hospitalization				
Mood disorders/Anxiety/Obsessive thinking	2 (4.3)	0 (0.0)	0.127	0.722
Thought disorders/psychotic symptoms	19 (41.3)	16 (59.3)	1.537	0.215
Impulsivity/Impulse control disorder/Behavioral disorders	15 (32.6)	9 (33.3)	0.000	1.000
Suicide attempt/Suicidal ideation/Self-injurious behaviours	5 (10.9)	0 (0.0)	1.677	0.195
Eating disorders	3 (6.5)	1 (3.7)	0.000	1.000
Comorbid medical disorder				
No	39 (84.8)	22 (81.5)	0.002	0.968
Type of discharge				
Home+mental health service	31 (67.4)	24 (88.9)	3.154	0.076
Residency/Prison	10 (21.7)	3 (11.1)	0.687	0.407
Other psychiatric ward (different city)	5 (10.9)	0 (0.0)	1.677	0.195
Already taking medication (before the index hospitalization)				
Yes	33 (71.7)	14 (51.9)	2.131	0.144
	M (SD)	M (DS)	T	p=0.05
Age	40.02 (12.186)	41.93 (13.767)	-0.614	0.541
Length of stay	13.85 (10.045)	17.19 (11.997)	-1.275	0.207

n = number; M = mean; SD = standard deviation; χ^2 = Chi-square test; T = Student's t-test

Most of the re-hospitalised patients had no medical comorbidity (83.6%), were already in treatment at the mental health service (72.6%), were already taking medication at the time of the index hospitalisation (64.4%), that was generally a voluntary hospitalisation (53.4%), mainly for thought disorder and psychotic

features (47.9%). The average length of stay was 15.08±10.85 days, slightly higher than the length of stay of no re-hospitalised patients (14.63±11.67 days). These features did not shown to be statistically significantly related to a higher frequency of re-hospitalisation.

Rates of re-hospitalisation and antipsychotic therapy

The overall rate of re-hospitalisation for the oral AP formulation was 63.0%, whilst for the LAI formulation was 37.0% (see table 4). The difference between oral AP and LAI in terms of rates of re-hospitalization in the 24-month follow-up was not found to be statistically significant.

As for the analysis of re-hospitalisation rates for the specific classes of AP (typical or atypical) (see table 5), 26.0% of patients were discharged with a typical LAI whilst the rate of re-hospitalisation of discharged patients with atypical LAI was 11.0%, without a statistically significant difference between the two sub-groups.

As for the oral formulation, the patients discharged with an atypical oral AP (34.2%) have the higher rate of re-hospitalisation, followed by 16.4% for typical oral AP and by 12.3% for the concomitant use of typical and atypical oral AP. The differences between re-hospitalised and not re-hospitalised patients were not statistically significant.

Re-hospitalisation: oral antipsychotic versus LAI

The impact of the patient's socio-demographic characteristics and the aspects related to hospitalisation on the choice of the therapeutic formulation (oral versus LAI) at the time of discharge was evaluated for the re-hospitalised patients (n=73) (see table 6). The re-hospitalised patients prescribed with LAI were mainly Italian (70.4%), males (59.3%), single (70.4%), with a mean age of 41.93 ± 13.77 years, slightly greater than the average age of patients requiring the oral formulation (40.02 ± 12.19 years), but the difference was not statistically significant ($p=0.541$). Patients discharged with LAI did not differ significantly from those prescribed with oral AP for gender, nationality, marital status, and age.

Most of the re-hospitalised patients who had been prescribed therapy with LAI did not report a medical comorbidity (81.5%), were already in treatment at the mental health service (77.8%), were already taking medication at the time of the index hospitalisation (51.9%), that was generally an involuntary hospitalisation (51.9%), mainly for thought disorder and psychotic features (59.3%). The average length of stay was 17.19 ± 12.0 days, higher than the length of stay of re-hospitalised patients prescribed with oral AP (13.85 ± 10.05 days) but not statistically significant ($p=0.207$). These features did not shown to be statistically significantly related to the choice of prescribing an oral AP versus a LAI formulation.

DISCUSSION

The rate of re-hospitalisation in this retrospective observational cohort study was not related with socio-demographic and clinical characteristics of the patients, with the type of the formulation of the prescribed AP (LAI versus oral) or with the specific category of AP (typical versus atypical).

Previous studies reported that the rate of re-hospitalisation was inversely correlated with age (Huang et al. 2013). Higher rates were reported for males and patients living alone (Doering et al. 1998). Even though previous data suggested that the re-hospitalisation was less likely to occur in patients using community psychiatric services (Song et al. 1998), the results of the current study underlined that the use of community services was not significantly related with the rates of re-hospitalisation. In addition, the risk of re-hospitalisation was not correlated neither with the type of hospitalisation (involuntary versus voluntary) nor with the characteristics of hospitalisation (i.e. length of stay, pharmacological treatment before being admitted to the hospital).

Other factors, such as substance abuse (Green 2006), a previous hospitalisation (Song et al. 1998) and comorbid depressive disorder (Siris 2000) may result in an increase in the rate of re-hospitalisation. Literature data are not in favour of a correlation between the severity of the disease and increased risk of re-hospitalisation (Üçok et al. 2006). On the contrary, adherence to pharmacological treatment is the most important predictor of relapse (Doering et al. 1998, Sullivan et al. 1995).

As for the type of prescribed formulation, in this study 34.3% of the patients (n=67) at discharge was prescribed with a LAI. This is in line with previous literature (Graffino et al. 2014) and might underline a general underutilization of LAI (Patel et al. 2009). Oral AP were associated with a higher rate of re-hospitalisation (63.0%) than LAI formulation (37.0%), even though the difference in the rates of re-hospitalisation within 24 months of follow-up were not statistically significant. These results confirm previous findings about the lack of a statistically significant difference in efficacy between LAI and oral AP in previous naturalistic studies (Marchiaro et al. 2005, Huang et al. 2013) and seem to be in line with data from recent randomized clinical trials reporting no difference between the two formulations in preventing the re-hospitalisation (Buckley et al. 2015, Fusar-Poli et al. 2013, Kishimoto et al. 2013, Rosenheck et al. 2011). Nonetheless, previous findings are conflicting. In fact, other studies highlighted a clear and significant superiority of LAI in preventing re-hospitalisation (Leucht et al. 2011, Olivares et al. 2009, Tiihonen et al. 2006, Tiihonen et al. 2011, Zhu Et al. 2008) whilst two prospective observational studies reported the superiority of the oral formulation in preventing recurrence and re-hospitalisation (Conley et al. 2003, Haro et al. 2006). The discrepancies between studies could be explained by the studies' designs and methodology. In general, not compliant patients are not selected and maybe do not agree to voluntarily participate in randomized clinical trials that are characterized by rigorous inclusion criteria (Haddad et al. 2009). On the contrary, naturalistic studies, as suggested by recent literature (Kishimoto et al. 2013, Kishimoto et al. 2014, Tiihonen et al. 2011), could better highlight differences between LAI and oral

AP in the every-day clinical practice, with a "real world" perspective.

The most important advantage in prescribing LAI is to ensure stable plasma levels of the antipsychotic medication, overcoming problems related to drug non-adherence (De Risio & Lang 2014). Indeed, it is reasonable to think that the injectable formulations are responsible for the prevention of relapse related to non-compliance. Assuming that in this study LAI have been prescribed mainly to those patients that were less adherent to oral therapy but considering a good organization of the territorial services which is essential in the effectiveness of LAI (Johnson 2009), it can be hypothesized that LAI could be as effective as their oral counterpart in predicting recurrence (De Risio & Lang 2014, Suzuki 2016, Taylor - KY 2013). Unfortunately, we did not find a statistically significant difference between the two formulations in terms of efficacy. Furthermore, the lack of prospective studies comparing oral AP and LAI do not allow drawing conclusions (Graffino 2014).

In the post-hoc secondary analysis of re-hospitalisation rates on the basis of the type of prescribed AP (typical or atypical), patients prescribed with oral atypical AP showed a higher rate of re-hospitalisation, followed by typical AP and finally by the co-administration of typical and atypical AP but the differences between the type of oral AP were not statistically significant. This finding is in line with recent studies underlining that there are no apparent differences in efficacy between first and second generation oral AP (Leucht 2009). Similar findings regarding the rates of re-hospitalisation in patients treated with typical or atypical oral AP have also emerged from recent retrospective observational studies (Herceg 2008, Werneck 2011). Except for clozapine that is the only AP indicated for resistant schizophrenia (Chakos 2001, McEvoy 2006), recent large randomized clinical trials such as the CATIE (Lieberman 2005), the CutLASS (Jones 2006) and the EUFEST (Kahn 2008) did not show differences in effectiveness between different AP. Recent international guidelines also show that both first and second generation AP are heterogeneous classes of globally comparable efficacy drugs with different specific characteristics and side effects (Hasan 2012).

As for the LAI formulation, in the present study a higher rate of re-hospitalisation with typical LAI (26.0%) and a lower rate with atypical LAI (11.0%) were found. Again, the differences between the rate of re-hospitalisation of patients treated with typical LAI or atypical LAI were statistically non-significant. There are relatively few studies comparing the efficacy of first and second-generation LAI in literature (Brissos 2014). A recent randomized, double-blind clinical trial (McEvoy 2014) and a recent retrospective cohort study (Nielsen 2015) did not find statistically significant differences in efficacy between first and second generation LAI.

Limitations

This study has limitations. First of all, the small sample could have limited the study, which in any case is intended to be a pilot study for subsequent large-scale re-evaluations. Furthermore, patients who have been discharged with LAI often require in the early stages of the treatment a "supplement" of oral AP of the same medication. Sometimes, once the patient has improved, the clinical tendency is to keep the therapeutic regimen (LAI and oral) unchanged, presumably to avoid the risk of recurrence (Taylor 2002). Finally, the severity of the disease was not evaluated with a structured evaluation, which did not allow us to assess whether the decision of prescribing the LAI formulation could depend on the patient's psychopathological state.

CONCLUSIONS

In this retrospective cohort study on the rates of re-hospitalisation in psychotic spectrum disorders it emerged that long-acting injectable antipsychotics are not superior than the oral formulations during a 24-month follow-up period in terms of efficacy in preventing recurrency. Since literature data remain conflicting, it is important to develop further clinical studies, not only randomized trials but also with an observational study design, in order to have a "real life" picture of long-acting injectable and oral antipsychotic treatment efficacy and tolerability.

Despite presenting differences in side effects and in the tolerability profile, both first and second generation antipsychotic seem to be two large heterogeneous classes of medications with comparable effectiveness in preventing re-hospitalisation.

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Contribution of individual authors:

Vincenzo Sicilia: made substantial contributions to the acquisition of data and participated in drafting the article.

Valentina del Bello: made substantial contributions to conception and design of the research project, participated in drafting the article and in revising it critically for important intellectual content.

Norma Verdolini: made substantial contributions to conception and design of the research project, to the analysis and interpretation of data, participated in drafting the article and in revising it critically for important intellectual content.

Alfonso Tortorella: made substantial contributions to conception and design of the research project, participated in revising the draft critically for important intellectual content and gave final approval of the version to be submitted and any revised version.

Patrizia Moretti: made substantial contributions to conception and design of the research project, participated in revising the draft critically for important intellectual content.

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