

EFFECT OF AN INSTITUTIONAL MEDICATION ADHERENCE PROGRAM FOR LONG-ACTING INJECTABLE RISPERIDONE ON ADHERENCE AND PSYCHIATRIC HOSPITALIZATIONS: EVIDENCE FROM A PROSPECTIVE COHORT STUDY

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Abstract

Background

Long-acting injectable (LAI) atypical antipsychotics are associated with improved adherence and reduced relapse rates in schizophrenia but reminder-based interventions may further improve outcomes.

Objectives

To assess an institutional medication adherence program's (IMAP) effectiveness on adherence and psychiatric hospitalizations among schizophrenia patients taking risperidone LAI (RLAI).

Methods

Between 2009 and 2010, we recruited patients meeting DSM-IV criteria for schizophrenia treated with RLAI receiving outpatient care from psychiatric centres in France. The IMAP consisted of calling patients 48 hours prior to their scheduled RLAI injections and within 3 days of a missed appointment. Centres applying the IMAP to $\geq 50\%$ of scheduled patient injections were deemed compliant. Patients were followed up to one year for adherence ($\geq 80\%$ of scheduled RLAI injections received within 5 days of the scheduled date) and psychiatric hospitalizations.

Results

Among 506 patients recruited from 36 centres, the hospitalization rate was 32.5 per 100 person-years. 15 centres treating 243 patients were IMAP compliant and 21 centres treating 263 patients were not. IMAP compliance was associated with lower psychiatric hospitalization rates (crude RR: 0.64 [95% CI: 0.44–0.93]; adjusted RR: 0.78 [95% CI: 0.47–1.27]). Nearly 75% of patients were adherent to RLAI. While patient

adherence had little impact on hospitalization rates (adjusted RR: 0.92 [95% CI: 0.59–1.44]), IMAP compliance was more effective among non-adherent (adjusted RR: 0.45 [95% CI: 0.16–1.28]) than adherent (adjusted RR: 0.88 [95% CI: 0.51–1.53]) patients.

Conclusions

IMAPs may improve patient adherence and reduce psychiatric hospitalizations, particularly among patients with difficulties adhering to LAI antipsychotics.

Antipsychotic medications are the cornerstone of schizophrenia treatment but non-adherence is a challenge in the management of the disease,¹ with estimates of non-adherence as high as 50%.^{2,3} Poor adherence is associated with worse prognosis as well as greater risks of psychiatric hospitalizations, emergency psychiatric services use, relapse, and suicide attempts.⁴⁻⁶

Implementing strategies targeting modifiable factors influencing adherence to antipsychotic medication is key to avoiding adverse consequences of non-adherence. The introduction of second generation long-acting injectable (LAI) antipsychotics in the mid-2000s increased the possibility of adherence by combining a more favourable neurologic safety profile than first generation LAIs with the persistence of first generation LAIs. LAIs are associated with greater adherence and persistence than oral antipsychotics but, unlike oral antipsychotics, LAIs are administered less frequently (i.e., bi-weekly or monthly versus daily) and are not self-administered, which may also impact adherence.⁷⁻¹⁰ Interventions incorporating reminders, cues, or reinforcements to take or refill medications are effective in enhancing adherence to oral antipsychotic medication¹¹⁻¹³ and phone appointment reminders may reduce non-attendance in psychiatric outpatient departments.¹⁴⁻¹⁶ The objective of this study was to evaluate the effectiveness of an institutional medication adherence program (IMAP), consisting of phone calls to remind patients of upcoming and of missed appointments, on adherence and psychiatric hospitalization rates among schizophrenia patients taking the LAI antipsychotic treatment, risperidone (RLAI).

METHODS

Design and Study Population

We randomly contacted by mail and then by phone, psychiatric centres or hospitals with a psychiatric ward across 17 French regions. In total, 104 physicians from

88 different centres were contacted, 71 physicians from 52 centres agreed to participate, and 44 physicians from 36 centres enrolled at least one patient in the study. Patient recruitment began in June 2009 and ended in May 2010, after 514 patients were recruited.

Eligible patients were those with a DSM-IV diagnosis of schizophrenia, aged 18 to 65 years, treated with RLAI, hospitalized for ≤ 3 months at enrolment, and receiving outpatient treatment from a participating psychiatric centre. Patients with limited life expectancy, enrolled in a clinical trial, not enrolled in the national health care system, or who did not understand French were not eligible.

Institutional Medication Adherence Program

The IMAP design was based on the hypothesis that more frequent interactions between schizophrenia patients and their health care providers could result in increased adherence and better outcomes. The IMAP consisted of having the primary provider call the patient within 48 hours of their scheduled RLAI injection. If the patient missed their appointment, the provider would call the patient within 3 days to remind them of their scheduled injection or, if the patient could not be reached, the patient's contact person. The IMAP was applied at the discretion of the centres.

Centres were categorized as IMAP-compliant if they applied the program, over the one year study period, to $\geq 50\%$ of their patients' scheduled RLAI injections, provided that information regarding IMAP application was available for $\geq 80\%$ of the scheduled RLAI injections for that centre. Centres not meeting these criteria were categorized as being not IMAP compliant.

Outcomes

Psychiatric hospitalization, a proxy for relapse, was defined as a hospitalization ≥ 24 hours in a psychiatric ward or for psychiatric reasons. Hospitalizations separated by less than seven days were considered to be related to the first hospitalization and counted once.

Patients were categorized as being adherent to RLAI if they had received $\geq 80\%$ of their scheduled injections within 5 days of the scheduled date over the one year study period. A cutoff of 80% was used to categorize patients as adherent to be consistent with the majority of studies on medication adherence¹⁷ and because it was endorsed by an expert consensus panel as an appropriate cutoff in schizophrenia.¹ If either the scheduled injection date or date of injection were missing, adherence to that RLAI injection could not be determined. Non-adherent patients were those for whom adherence could not be determined for $\geq 20\%$ of their scheduled injections or who showed up within 5 days of their scheduled injection date for $< 80\%$ of their RLAI injections.

Data Collection and Data Elements

At cohort entry, information on patient sociodemographics (age, sex, marital status [single vs. not], education [$<$ than high school vs. \geq high school], living arrangement [living independently vs. not], employment [working vs. not], and guardianship [yes/no]), DSM-IV schizophrenia type (paranoid, catatonic, disorganized, undifferentiated, residual), schizophrenia severity (past-year psychiatric hospitalizations, hospitalized at cohort entry, Clinical Global Impression-Severity [CGI-S] score [actual and lifetime maximum; range from 1 to 7 with higher scores indicating more severe disease], Brief Psychiatric Rating Scale [BPRS; range 18 to 126 with higher scores indicating greater symptom severity], Global Assessment of Functioning Scale [GAF; range from 0 to 100 with higher scores indicating greater functioning]), psychiatric comorbidities as per the Mini International Neuropsychiatric Interview (depression, bipolar disorder, anxiety disorders, alcohol or substance [marijuana, opioids, stimulants] abuse, suicidality [moderate or high]), number of past suicide attempts, smoking status (current vs. past/never), and somatic comorbidities (cardiovascular, endocrine, respiratory, musculoskeletal, or gastrointestinal diseases) were obtained from the patient's medical records. Current and past-year medication use was also collected at cohort entry, using the patient's medical record. Information was collected on dose and start date for individual antipsychotic medications and exposures were categorized according to generation (second vs.

first), duration of action (long vs. immediate acting), polytherapy (if exposed more than one antipsychotic), and time since RLAI initiation (> 30 days or ≤ 30 days). We also collected information on centre type (general vs. psychiatric) and proxies for centre size (i.e. number of schizophrenia patients treated by the centre and number of beds in the ward).

In addition to the elements mentioned above, data on mortality (date and cause) and psychiatric hospitalizations (number and duration) were collected at 3, 6, 9, and 12 months from the patient's medical record.

Follow-Up

Patients were followed from cohort entry to 12 months, death, or loss to follow-up. In accordance with a previously described methodology,¹⁸ follow-up during any given trimester (i.e., 3 months) was categorized as indefinite if data on hospitalizations and antipsychotic use was missing. Trimesters categorized as indefinite were not included in the follow-up but patients could re-enter the cohort during subsequent trimesters.

Statistical Analysis

Patient characteristics are reported for the cohort as well as by IMAP compliance and patient adherence using percentages for categorical variables and means and standard deviations and/or medians and 25% and 75% percentiles for continuous variables. Characteristics of centres participating in the study are also reported.

We calculated psychiatric hospitalization rates per 100 person-years as the number of psychiatric hospitalizations divided by the number of person-years at risk of hospitalization multiplied by 100, with 4 trimesters roughly equivalent to one person-year. We estimated hospitalization rates and calculated 95% confidence intervals (CI) overall and by IMAP compliance and patient adherence. Using Poisson regression, we report unadjusted relative rates (RR) and 95% CIs comparing patients treated in IMAP-compliant versus non-compliant centres and adherent versus non-adherent patients. To derive adjusted estimates, we built separate propensity scores for IMAP-compliance (patients treated at IMAP compliant vs. non-compliant centres) and adherence (yes vs. no), including sociodemographics, schizophrenia severity, psychiatric comorbidities,

suicidality, somatic comorbidities, antipsychotic use, and centre-level variables. Propensity scores were categorized into quintiles and included directly in the Poisson regression model. We assessed the possibility of an interaction between IMAP compliance and patient adherence by deriving stratified estimates and by including an interaction term in the model. When missing data was <10%, we imputed the mean for continuous variables and the mode for categorical variables and when $\geq 10\%$ of data were missing for a given variable, we included a level representing the missingness in the outcome model. All analyses were conducted using SAS[®] 9.3 (SAS Institute, Cary, NC).

Ethics

The study was conducted in accordance with ethical principles stated in the Declaration of Helsinki and was approved by the French privacy and data protection authority and the French national board of physicians. Informed consent was obtained from patients or from the patient's guardian.

RESULTS

Of the 84 centres that were contacted, 52 (61.9%) accepted to participate in the study and 36 (69.2%) followed up at least one patient. Participating centres were predominantly general (vs. psychiatric) centres (68.6%), treating a mean of 250.1 (Standard Deviation [SD]:195.1) schizophrenia patients, had a mean of 25.4 (SD: 13) beds, and >80% were located outside the Paris region. The mean number of patients recruited per centre was 14.5 (SD: 12.1; range: 1–49).

In total, 514 patients were enrolled, 506 (98.4%) were followed-up and 492 (95.7%) followed up to 12 months. Patients had a mean age of 38.7 years (SD: 11.0), 64.6% were male, 72.1% had less than a high school education, 21.1% were working, 61.7% were living independently, (Table 1). The predominant form of schizophrenia was paranoid (62.3%) and 60.4% had a past-year psychiatric hospitalization. There were 163 hospitalizations over 502 patient-years of follow-up. The rate of psychiatric hospitalizations per 100 person-years was 32.5 (95% [CI]: 27.7 to 37.9).

Of the 36 centres, 15 (41.7%) centres treating 243 (48.0%) patients were categorized as IMAP-compliant and 21 (58.3%) centres treating 263 (52.0%) patients were categorized as being IMAP non-compliant. Of

the non-compliant centres, 5 centres treating 31 patients did not provide sufficient data to categorize their compliance, including 2 centres which provided no data. Compared to compliant centres, non-compliant centres were less likely to be specialized in psychiatry (45.5% vs. 54.5%) and had a smaller mean number of psychiatric hospital beds (23.8 vs. 28.6).

Patients treated by IMAP-compliant compared to non-compliant centres were less likely to be living independently (56.4% vs. 66.5%) and currently working (18.5% vs. 23.6%) but were more likely to be on antipsychotic monotherapy (60.5% vs. 54.0%) (Table 1). Patients treated by IMAP-compliant centres also had lower proportions of patients using all antipsychotic classes, and maximum lifetime CGI-S, BPRS, and GAF scores indicative of slightly lower schizophrenia severity.

Overall, 368 (72.3%) patients were categorized as adherent to their RLAI regimen. Of the 138 patients categorized as non-adherent, adherence could not be determined for more than 20% of reported scheduled RLAI injections for 62 patients (44.9%). Non-adherent patients appeared to be slightly healthier than adherent patients as they were more likely to be working (24.6% vs. 19.8%) and less likely to have been hospitalized in the past-year (53.2% vs. 63.3%) (Table 1). Mean scores on the maximum lifetime CGI-S, BPRS, and GAF were comparable across adherence as was antipsychotic use.

Patients treated in IMAP-compliant centres had lower psychiatric hospitalization rates per 100 person-years (25.3; 95% CI: 19.3–32.4) than patients treated by centres who were not compliant (39.2; 95% CI: 32.0–47.6) (Table 2). The effect of IMAP compliance on reducing hospitalization rates persisted after adjusting for patient- and provider-level variables (RR=0.78; 95% CI: 0.47–1.27). Unadjusted psychiatric hospitalizations rates per 100 person-years were 32.8 (95% CI: 27.2–39.2) and 31.7 (95% CI: 23.0–42.7) among adherent and non-adherent patients, respectively (Table 2). The RR of psychiatric hospitalizations after adjustment for patient- and provider-level factors was 0.92 (95% CI: 0.59–1.44).

The effect of IMAP-compliance differed by adherence. Among adherent patients ($N=368$), patients treated in IMAP-compliant centres had lower hospitalization

TABLE 1 Baseline Patient Characteristics Overall and Stratified by Centre IMAP Compliance and Patient Adherence

Patient Characteristics	Centre IMAP Compliance		Patient Adherence		All
	IMAP-Compliant (n=243)	Not IMAP-Compliant (n=263)	Adherent (n=368)	Non-Adherent (n=138)	Total (n=506)
Sociodemographics					
Mean age in years (SD)	37.2 (10.9)	40.1 (11.0)	38.2 (11.0)	40.1 (11.2)	38.7 (11.0)
Men	166 (68.3%)	161 (61.2%)	246 (66.8%)	81 (58.7%)	327 (64.6%)
Less than high school education	160 (65.8%)	205 (77.9%)	261 (70.9%)	104 (75.4%)	365 (72.1%)
Currently working	45 (18.5%)	62 (23.6%)	73 (19.8%)	34 (24.6%)	107 (21.1%)
Single marital status	188 (77.4%)	178 (67.7%)	269 (73.1%)	97 (70.3%)	366 (72.3%)
Living independently	137 (56.4%)	175 (66.5%)	225 (61.1%)	87 (63.0%)	312 (61.7%)
No guardianship	188 (77.4%)	182 (69.2%)	275 (74.7%)	95 (68.8%)	370 (73.1%)
Schizophrenia Subtype					
Paranoid	166 (68.3%)*	154 (58.6%)*	246 (66.8%)*	74 (53.6%)	320 (63.2%)*
Catatonic	0 (0.0%)*	6 (2.3%)*	2 (0.5%)*	4 (2.9%)	6 (1.2%)*
Disorganized	19 (7.8%)*	35 (13.3%)*	33 (9.0%)*	21 (15.2%)	54 (10.7%)*
Undifferentiated	41 (16.9%)*	49 (18.6%)*	65 (17.7%)*	25 (18.1%)	90 (17.8%)*
Residual	17 (7.0%)*	18 (6.8%)*	21 (5.7%)*	14 (10.1%)	35 (6.9%)*
Proxies of Schizophrenia Severity					
At least one past-year hospitalization	111 (64.2%)†	116 (57.1%)‡	169 (63.3%)†	58 (53.2%)‡	227 (60.4%)†
Maximum lifetime mean CGI-S score (SD)	5.3 (0.9)	5.6 (0.9)	5.5 (0.9)	5.5 (0.8)	5.5(0.9)
Min-Max	2-7	2-7	2-7	3-7	2-7
Mean BPRS score (SD)	37.5 (13.3)*	43.5 (16.1)	39.7 (14.4)*	43.1 (16.5)	40.6(15.1)*
Min-Max	18-76*	18-99	18-93*	18-99	18-99*
Mean GAF score (SD)	63.3 (13.5)	56.3 (15.8)	60.9 (14.3)	56.2 (16.8)	59.6(15.2)
Min-Max	20-90	5-91	20-91	5-90	5-91
Antipsychotic Use					
30 days or less since long-acting risperidone initiation	53 (22.3%)§	64 (24.9%)§	90 (24.9%)§	27 (20.3%)§	117 (23.6%)§
Second generation immediate acting antipsychotic	48 (19.8%)	64 (24.3%)	83 (22.6%)	29 (21.0%)	112 (22.1%)
First generation long-acting antipsychotic	2 (0.8%)	5 (1.9%)	6 (1.6%)	1 (0.7%)	7 (1.4%)
First generation immediate acting antipsychotic	50 (20.6%)	79 (30.0%)	90 (24.5%)	39 (28.3%)	129 (25.5%)
Antipsychotic monotherapy	147 (60.5%)	142 (54.0%)	213 (57.9%)	76 (55.1%)	289 (57.1%)

Abbreviations: CGI-S=Clinical Global Impression-Severity; BPRS=Brief Psychiatric Rating Scale; GAF=Global Assessment of Functioning; IMAP=Institutional Medication Adherence Program; SD=Standard Deviation.

*<1% missing; †25-30% missing; ‡20-25% missing; §1-5% missing

TABLE 2 Rates of Psychiatric Hospitalization and Relative Rates of Hospitalization by Centre-IMAP Compliance and Patient Adherence

	Number of Events/ Person-Years	Psychiatric Hospitalization Rates per 100 Person-Years (95% CI)	Unadjusted Relative Rate (95% CI)	Adjusted Relative Rate (95% CI)
Center IMAP Compliance				
Compliant	61/242	25.3 (19.3 to 32.4)	0.64 (0.44 to 0.93)	0.78* (0.47 to 1.27)
Not Compliant	102/260	39.2 (32.0 to 47.6)	Referent	Referent
Patient Adherence				
Adherent	120/366	32.8 (27.2 to 39.2)	1.02 (0.68 to 1.52)	0.92* (0.59 to 1.44)
Non-Adherent	43/136	31.7 (23.0 to 42.7)	Referent	Referent

CI = confidence interval; IMAP=Institutional Medication Adherence Program.

*Adjusted for the quintiles of the propensity score considering all variables listed in Table 1 as well as hospitalized at cohort entry, psychiatric comorbidities (depression, bipolar disorder, anxiety disorders, alcohol or substance abuse, suicidality, smoking status) number of past suicide attempts, smoking status, somatic comorbidities (cardiovascular, endocrine, respiratory, musculoskeletal, or gastrointestinal diseases), region where center was located, number of psychiatric hospital beds, and type of centre.

rates per 100 person-years (28.2; 95% CI: 21.3–36.6) than patients treated in centres that were not compliant (38.3; 95% CI: 29.5–48.9) (Table 3). Among non-adherent patients ($N=138$), the effect of IMAP compliance on psychiatric hospitalization per 100 person-years was more pronounced (11.7; 95% CI: 3.8–27.3 vs. 41.0; 95% CI: 29.0–56.2). The adjusted RRs comparing patients treated in IMAP compliant vs. non-IMAP-compliant centres for adherent patients (RR=0.86; 95% CI: 0.48–1.55) was more than double that for non-adherent (RR=0.40; 95% CI: 0.12–1.27) patients. When modelled, the interaction between IMAP compliance and patient adherence achieved borderline significance (p -value=0.07 with and without covariate adjustment).

Sensitivity Analysis

When the analysis was restricted to centres whose IMAP compliance was known and to patients whose adherence was known, power was reduced but results were generally robust (Supplemental Table 1). When the criteria to categorize centres as IMAP compliant was raised from applying the intervention to 50% or more of their patients' scheduled RLAI injections to 80%, the effect of the IMAP increased only slightly (Supplemental Table 2).

DISCUSSION

In this prospective cohort study, we found that a telephone call reminding patients of an upcoming appointment for their antipsychotic injection and a follow-up call in case of a missed appointment resulted in high level of adherence (almost 75% over 1 year) among schizophrenia patients taking RLAI, treated in the outpatient setting. This intervention was also associated with a reduction in the rate of psychiatric hospitalizations. The intervention may have been more effective at reducing psychiatric hospitalizations among patients who were non-adherent to their LAI regimen.

The proportion of patients who were categorized as adherent was high: nearly 75% over one year of follow-up. The true level of adherence in our study is likely higher as almost half (44.9%) of patients whose adherence could be determined were classified as non-adherent. The level of adherence observed in our study is much higher than the level of LAI adherence reported in a recent study. Among Medicaid schizophrenia patients, adherence (measured as proportion of days covered as ≥ 0.80) in the 6-month period following a schizophrenia-related hospitalization was 42.8% for any LAI ($N=340$) and, slightly higher, 52.5% ($N=183$) for second generation LAIs.¹⁹ The proportion of Medicaid patients who continue to be

TABLE 3 Interaction of Center-IMAP Compliance and Patient Adherence on Psychiatric Hospitalizations

	Psychiatric Hospitalization Rates per 100 Person-Years (95% CI)	Unadjusted Relative Rate (95% CI)	Adjusted Relative Rate (95% CI)
Adherent Patients (N=368)			
Compliant Center (N=200)	28.2 (21.3 to 36.6)	0.73 (0.47 to 1.15)	0.86* (0.48 to 1.55)
Not Compliant Center (N=168)	38.3 (29.5 to 48.9)	Referent	Referent
Non-Adherent Patients (N=138)			
Compliant Center (N=43)	11.7 (3.8 to 27.3)	0.29 (0.12 to 0.70)	0.40* (0.12 to 1.27)
Not Compliant Centers (N=95)	41.0 (29.0 to 56.2)	Referent	Referent

CI = confidence interval; IMAP = Institutional Medication Adherence Program.

*Adjusted for the quintiles of the propensity score considering all variables listed in Table 1 as well as hospitalized at cohort entry, psychiatric comorbidities (depression, bipolar disorder, anxiety disorders, alcohol or substance abuse, suicidality, smoking status) number of past suicide attempts, smoking status, somatic comorbidities (cardiovascular, endocrine, respiratory, musculoskeletal, or gastrointestinal diseases), region where center was located, number of psychiatric hospital beds, and type of centre

adherent to their LAI regimen at 12 months is likely to be lower. While we cannot confirm that the high level of adherence in our study is due to the IMAP, our findings suggest that the intervention likely had a positive effect on patient adherence.

LAI have been shown to decrease rates of relapse/psychiatric hospitalizations compared to oral antipsychotics in randomized controlled trials (RCTs),²⁰ meta-analyses of RCTs,²¹ and observational studies of schizophrenia outpatients.^{7,18,22,23} Some studies, however, have failed to demonstrate advantages of LAIs versus oral antipsychotics on relapse/hospitalization rates,²⁴ including RCTs.^{25,26} This discrepancy may be attributable to attenuating differences in adherence between LAI and oral antipsychotic users; in RCTs, non-adherent patients may be underrepresented,²⁷ in inpatient settings adherence will be more closely controlled than in outpatient settings, and, in outpatient settings, changes from daily to bi-monthly or monthly administrations may negatively influence adherence for patients who have difficulties remembering appointments and managing their time. Reminder-based interventions can address the latter source of non-adherence, which may be due to symptoms of schizophrenia such as disorganization, lack of insight, or cognitive dysfunction rather than a lack of willingness to take medications. Indeed, in

this study, patient support in the form of well-timed, direct phone calls was associated with a reduction in psychiatric hospitalization rates. In addition, the effect of the IMAP appeared to be greater among non-adherent patients, who also tended to have a higher prevalence of disorganized schizophrenia and greater symptom severity. A complementary strategy to improve adherence and, concomitantly, outcomes in schizophrenia outpatients treated with LAIs may therefore consist of reminder phone calls for appointments and follow-up phone calls for no-shows.

The results of this study must be interpreted in the context of certain limitations. Firstly, IMAP compliance and patient adherence data was not always complete; IMAP compliance could not be determined for centres treating approximately 6% of patients and adherence could not be determined for 12% of patients. The results of our sensitivity analyses, however, suggest that centres not collecting information on their application of MAP were unlikely to be compliant since removing patients whose adherence was unknown did not have a substantial impact on the estimates. Another limitation of this study was the lack of power; likely due to the success of the intervention, there were few patients who were non-adherent (<150 patients), which limited the ability to detect a significant interaction between IMAP compliance and patient adherence. The

effectiveness of the intervention was evaluated over a one-year period and it is unclear whether “reminder fatigue” would attenuate the effectiveness of the IMAP over longer periods, such as 2, 5, or 10 years. Lastly, the IMAP does not address non-adherence stemming from reasons other than lack of illness insight or forgetfulness (e.g., side effects, drug resistance, centre experience with LAI administration) and residual confounding cannot be ruled out.

Ours is one of only a handful of studies evaluating interventions to improve adherence to LAIs^{28,29} and the first to assess the effectiveness of a reminder-based intervention. We evaluated the effect of an intervention on over 500 patients, which were followed for one year with very little attrition. We collected data such that we could evaluate and control for factors known to affect adherence, such as sociodemographics, disease severity, social support, and alcohol/substance abuse.² Lastly, we applied broad inclusion and few exclusion criteria in order to ensure that the results of this study would be generalizable to the French outpatient schizophrenia population treated with LAIs.

Adherence may be modifiable risk factor for relapse but it often goes undetected. While adherence to LAIs may be higher than with oral antipsychotics, we demonstrated that outcomes among schizophrenia outpatients taking LAIs can be further improved by implementing an IMAP consisting of a telephone-based intervention, particularly among patients with difficulties adhering to their treatment regimen. One of the main advantages of LAIs is that non-adherence is immediately noticeable through direct refusal or missed appointments but it does not address non-adherence stemming from deficiencies in attention and memory. Calling patients to remind them of an upcoming appointment or following up with them via phone in case of a missed appointment serves as both a reminder and as reinforcement to adhere to LAI therapy. Outpatient care for schizophrenia could be improved by implementing a telephone-based IMAP for patients taking LAIs, as a relatively low cost, low burden strategy to improve adherence and avoid costly hospitalizations due to relapse. Future studies should evaluate the cost-effectiveness of the program, assess effectiveness of reminders using text messaging, and explore barriers to program implementation at centres.

CONFLICTS OF INTEREST

Drs. JJJ, MR, CN, and LGB are employees of Analytica LASER, which received funding from Janssen-Cilag to conduct this study, Drs. BAst and BA_v were consultants to Analytica LASER during the conduct of the study, Dr. FB has received grants from Janssen France, has served on the board for Shire, Novartis, and Servier, and has participated in symposia with Janssen, Servier, and Shire, Dr. FR has served as a consultant to Janssen, and Dr. LA is stockholder and chairman of Analytica LASER.

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SUPPLEMENTAL TABLE 1 Rates of Psychiatric Hospitalization and Relative Rates of Hospitalization by Centre-IMAP Compliance and Patient Adherence, when Compliance and Adherence Are Known

	N Events	Person-years	Psychiatric hospitalization rates per 100 person-years	95% CI	Unadjusted RR	95% CI	Adjusted RR	95% CI
Center IMAP compliance								
Compliant (N=243)	61	242	25.3	19.3-32.4	0.75	0.50-1.13	0.81 ^a	0.39-1.71
Not compliant (N=232)	77	230	33.5	26.4-41.8	Referent		Referent	
Patient adherence								
Adherent (N=368)	120	366	32.8	27.2-39.2	1.05	0.65-1.69	1.05 ^a	0.57-1.93
Non-adherent (N=76)	23	75	30.8	19.5-46.2	Referent		Referent	

CI = confidence interval; IMAP = Institutional Medication Adherence Program

^aAdjusted for the quintiles of the propensity score considering all variables listed in Table 1 as well as hospitalized at cohort entry, psychiatric comorbidities (depression, bipolar disorder, anxiety disorders, alcohol or substance abuse, suicidality), smoking status, number of past suicide attempts, smoking status, somatic comorbidities (cardiovascular, endocrine, respiratory, musculoskeletal, or gastrointestinal diseases), region where center was located, number of psychiatric hospital beds, and type of centre

SUPPLEMENTAL TABLE 2 Rates of Psychiatric Hospitalization and Relative Rates of Hospitalization by Centre-IMAP compliance when IMAP is applied to ≥80% of Scheduled RLAI Injections

	N Events	Person-years	Psychiatric hospitalization rates per 100 person-years	95% CI	Unadjusted RR	95% CI	Adjusted RR	95% CI
Center IMAP compliance								
Compliant (N=142)	42	140.5	29.9	21.5-40.4	0.89	0.59-1.33	0.69 ^a	0.41-1.15
Not compliant (N=364)	121	361	33.5	27.8-40.0	Referent		Referent	

CI = confidence interval; IMAP = Institutional Medication Adherence Program

^aAdjusted for the quintiles of the propensity score considering all variables listed in Table 1 as well as hospitalized at cohort entry, psychiatric comorbidities (depression, bipolar disorder, anxiety disorders, alcohol or substance abuse, suicidality), smoking status, number of past suicide attempts, smoking status, somatic comorbidities (cardiovascular, endocrine, respiratory, musculoskeletal, or gastrointestinal diseases), region where centre was located, number of psychiatric hospital beds, and type of centre.