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Predictive factors of functional remission in patients with early to mid-stage schizophrenia treated by long acting antipsychotics and the specific role of clinical remission

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ABSTRACT

Background: Functional remission has become a major therapeutic objective in schizophrenia, but the probability of such positive outcome has a large variability, ranging from 15% to 51%. Additionally, how clinical remission constitutes a prerequisite for functional remission also remains unclear.

Methods: A prospective observational study was conducted in French schizophrenic patients who initiated treatment with a long-acting injectable (LAI) after an acute episode. Functional and clinical remissions were assessed using the FROGS and the Andreasen criteria, and the role of clinical remission and predictive factors of functional remission was evaluated.

Results: Three hundred three patients with schizophrenia (DSM-IV criteria) were followed for 12 months. At 12 months, 45.1% of the patients reached functional remission while 55.1% obtained clinical remission. Clinical remission facilitated functional remission (OR = 14.74), especially in patients with psychosis for less than 5 years (OR = 23.73). Other predictive factors concerned the family environment, education level, employment status, baseline functioning levels and level of insight.

Conclusions: About half of patients treated with LAI reached functional remission after one year of follow-up. Reduced clinical symptoms and reaching clinical remission largely favored functional remission. These results stress the importance of continuous and appropriate symptomatic treatment to reach functional remission and maximize recovery chances.

1. Introduction

Schizophrenia is a chronic and severe disorder, affecting around 1% of the population and characterized by periods of acute episodes (Leucht et al., 2007; Millier et al., 2014; Tandon et al., 2013). During the course of the disease, patient disability increases due to residual psychotic symptoms of varying intensity (Heilbronner et al., 2016) and a diminution of functioning (Peuskens and Gorwood, 2012) which strongly impacts the prospect of recovery (Leucht, 2014; Liberman, 2012). Recent progress in pharmacological treatments and non-pharmacological care has set remission as the key goal in schizophrenia treatment (Leucht, 2014).

Remission includes different dimensions such as clinical (symptomatic) and functional remission (Andreasen et al., 2005). Clinical remission was defined by the Remission in Schizophrenia Working Group (RSWG) as a state of no greater than low-to-mild intensity in six core

Abbreviations: CGI-I, Clinical Global Impression-Improvement; EGOFORS, European Group On Functional Outcomes and Remission in Schizophrenia; EQ-5D, EuroQol-5D; FROGS, Functional Remission of General Schizophrenia; GAF, Global Assessment of Functioning; LAI, long acting injectable; PANSS-8, Positive and Negative Syndrome Scale-8 items; PSP, Personal and Social Performance; PSRS, Psychosocial Remission in Schizophrenia; RSWG, Remission in Schizophrenia Working Group; SWN, Subjective well-being under neuroleptic treatment

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psychotic symptoms, sustained for a minimum duration of six months (Andreasen et al., 2005). Functional remission in schizophrenia could be defined as the ability of patients to adapt to difficulties of societal life and reintegrate into their environment (Bodén et al., 2009; Peuskens and Gorwood, 2012). Functional remission is a complex entity, with various instruments (Figueira and Brissos, 2011), no consensus on the most appropriate way to assess it (Brissos et al., 2011; Peuskens and Gorwood, 2012; Mallet et al., 2018), and a variability ranging between 14.7% and 51% according to criteria and studies (AlAqeel and Margolese, 2012).

Different scales have indeed been developed to measure functional remission, including the Personal and Social Performance (PSP) (Morosini et al., 2000), the Global Assessment of Functioning (GAF) (Aas, 2011; Endicott et al., 1976), the Psychosocial Remission in Schizophrenia (PSRS) (Barak and Swartz, 2012) and the Functional Remission of General Schizophrenia (FROGS) (Llorca et al., 2009). The PSP and the GAF scales are nonspecific to schizophrenia (Llorca et al., 2009), whereas the PSRS is specific but focuses on psycho-social remission (Valencia et al., 2015). The FROGS is a specific, validated scale for the functional assessment of schizophrenia, which covers a large functional spectrum (Boyer et al., 2013; Lancon et al., 2012; Llorca et al., 2009; Rouillon et al., 2013) with 19 items clustered into three dimensions (i) social functioning (11 items), (ii) daily life (4 items) and (iii) treatment (4 items) (Gorwood et al., 2018).

Some standardized criteria (Alenius et al., 2010; Mosolov et al., 2014) were proposed to define functional remission, but they were scarcely used afterwards. Recently, a threshold to discriminate patients in functional remission using the FROGS was validated in patients with schizophrenia (Gorwood et al., 2018) facilitating the distinction between the presence versus the absence of functional remission in clinical practice.

Symptomatic remission is known to be frequently associated with improved functioning (Lambert et al., 2010), but only one-third of patients with clinical remission acquire functional remission (Bobes et al., 2009; Lambert et al., 2006; San et al., 2007; Wunderink et al., 2009). The relationship between symptomatic and functional remission therefore requires further investigation to characterize the key factors influencing patient prognosis to optimize patient care.

Several other predictive factors of functional remission have been proposed in the literature, including: (i) demographic aspects such as a younger age (Albert et al., 2011; Gould et al., 2012; Olsson et al., 2016; Schennach-Wolff et al., 2009; Spellmann et al., 2012), female gender (Albert et al., 2011; Olsson et al., 2016; Spellmann et al., 2012), growing up with both parents (Albert et al., 2011), having a job (Chan et al., 2018; Gorwood et al., 2018; Schennach et al., 2012; Schennach-Wolff et al., 2009; Spellmann et al., 2012; Valencia et al., 2015), and a stable social life (Albert et al., 2011; Spellmann et al., 2012); (ii) psychiatric history, such as earlier age of diagnosis (Austin et al., 2013), a first psychotic episode (Spellmann et al., 2012), a later age of onset (Spellmann et al., 2012), a shorter duration of psychosis (Carbon and Correll, 2014; Chan et al., 2018; Robinson et al., 2004; Schennach-Wolff et al., 2009; Spellmann et al., 2012), a reduced number of past hospitalizations (Gorwood et al., 2018; Spellmann et al., 2012) and less suicidality (Schennach-Wolff et al., 2009); (iii) clinical characteristics such as a low level of negative symptoms and/or neurocognitive impairment (Albert et al., 2011; Austin et al., 2013; Jordan et al., 2014; Lysaker and Davis, 2004; Milev et al., 2005; Robinson et al., 2004; Schennach-Wolff et al., 2009; Spellmann et al., 2012; Valencia et al., 2015), and better quality of insight (Alenius et al., 2010); (iv) therapeutic aspects, including good treatment adherence (Carbon and Correll, 2014; Novick et al., 2009), use of atypical antipsychotics (Valencia et al., 2015), being an early responder (Spellmann et al., 2012), and a reduced side effect burden of antipsychotic therapy (Weiden and Buckley, 2007).

The above rich domain of research provided non-homogenous results, which call for refining the key predictive factors of functional remission. The type of antipsychotic treatment and the route of administration are also important aspects that can be related to remission (clinical and functional). Lambert et al. (2006) found that a first-line treatment with atypical antipsychotics, compared to conventional antipsychotics, increases the likelihood of complete remission. In a trial devoted to long-acting injectable (LAI) antipsychotics for schizophrenia patients, Lambert et al. (2010) observed that the rate of functional remission (37.8%) at the end of the protocol (Global Assessment of Function > 60) was more frequent than the rate of stable symptomatic remission (33.3%). In a prospective observational study involving 1490 adult schizophrenia-spectrum chronic patients, previously treated with LAI for six months, clinical remission (using the Andreasen Criteria) and the level of functioning (using the GAF) were assessed after one year of LAI treatment (Giraud-Baro et al., 2016). 27.7% of patients were in clinical remission after one year of LAI treatment, with a mean GAF rating score (62.5 ± 1.5) higher than the cut-off previously used to identify patients with satisfactory functioning (GAF > 60) and significantly higher than the mean GAF score in stable, non-remitted patients (48.3, $p < 0.001$).

French guidelines recommend the use of LAIs for any patient for whom maintenance antipsychotic treatment is indicated, as early as the first psychotic episode (Samalin et al., 2013). Investigating predictive factors of functional remission in patients treated with LAI could therefore improve patient care by optimizing treatment decisions.

In this context, the present study was conducted to evaluate the frequency of functional remission in patients with schizophrenia treated with LAIs following an acute episode and to analyze predictive factors, with an emphasis on the role of clinical remission in fostering functional remission.

2. Methods

2.1. Study objectives

This study aimed to evaluate functional remission in early-to-mid-stage schizophrenia patients treated with LAI for an acute episode in a real-world setting and followed for 12 months after LAI initiation. The relationship between functional remission (Gorwood et al., 2018) and clinical remission (RSWG criteria) (Andreasen et al., 2005) was further investigated in these patients, as well as the predictive factors of functional remission.

2.2. Study design

This is a prospective observational study was conducted in France in 72 public and private investigational sites, by a total of 120 psychiatrists. The study was sponsored by JANSSEN CILAG (Issy-les-Moulineaux, France). The study was approved by French Regulatory Committees according to local regulation and was registered in ClinicalTrials.gov (Identifier: NCT02874560).

Inclusion criteria: Patients with schizophrenia (assessed by the DSM-IV criteria), aged 18–37 years-old and having initiated LAI treatment following an acute episode within the last two months were included in this study. LAI included any commercially available LAI treatment. The inclusion period lasted from August 29th, 2014 to July 15th 2016. Patients were followed for 12 months.

Additional inclusion criteria were: male or female patients who agreed to participate by signing an informed consent form, who have been followed for at least six months in the investigator's site (to ensure availability of patient's history), and who were expected to be followed by the same health care staff in the following year.

Exclusion criteria included treatment-resistant schizophrenia (defined as no response to two successive treatments administered with an effective dose for a minimum of four weeks); substance abuse (except nicotine or caffeine) or alcohol dependence; antecedents of neuroleptic malignant syndrome; inability to comply with the requirements of the

study (intellectual disability or inability to answer questionnaires); being under guardianship or psychiatric care without consent; patient participating or having participated in an interventional study in the 30 days prior to the inclusion in the study.

The evaluation period lasted 12 months and included three assessment visits: visit 1 (baseline); visit 2 (six months); visit 3 (end of the study, twelve months).

2.3. Data collection

The following data were collected in case report forms:

- Patient baseline demographics (age, sex, family situation, educational level, socio-professional status),
- Level and type of relationship with close relatives,
- Global medical history,
- Characteristics of schizophrenia, duration of disease, hospitalizations before and during the study,
- Study treatments: LAI initiation, changes during the study, compliance
- Concomitant medications and non-pharmacological treatments (psychotherapies, psychosocial care),
- Safety of sponsor drugs,
- Clinical assessments:
  - Positive and Negative Syndrome Scale-8 items (PANSS-8) scores (van Os et al., 2006) at baseline, 6 and 12 months,
  - Clinical Global Impression-Improvement (CGI-I) scale at 6 and 12 months,
- Functioning assessments (at baseline, 6 and 12 months):
  - FROGS scale scores (Llorca et al., 2009; Rouillon et al., 2013)
  - PSP scale scores (Morosini et al.; 2000).
- Patient insight and self-questionnaires:
  - Birchwood questionnaire (Birchwood et al., 1994)
  - Subjective well-being under neuroleptic treatment (SWN) scale (Naber, 1995; Naber et al., 2001)
  - EuroQol-5D (EQ-5D) scale (EuroQol, 1990)

2.4. Analysis

2.4.1. Primary analysis

Functional remission, and its relationship with clinical remission, were evaluated at 12 months using a French version of the FROGS scale (Rouillon et al., 2013). Functional remission was defined as a sub-score ≥ 33 on the first factor of the FROGS (social functioning) and sub-scores of ≥ 12 on the second (daily life) and third (health and treatment) factors (Gorwood et al., 2018). Clinical remission was evaluated using the RSWG consensus criteria (Andreasen et al., 2005), i.e., a state of no greater than "mild" intensity on the PANSS-8 core psychotic symptoms (van Os et al., 2006) for at least six months.

2.4.2. Secondary analysis

- Functional remission was analyzed at 12 months according to the following baseline variables: clinical status measured by the PANSS-8 scores, psychosocial remission (PSP scale), clinical global impression (CGI scale), insight (Birchwood scale), wellbeing (SWN) scale, health-related quality of life (EuroQol-5D scale), demographic characteristics (age, sex, socio-professional status and family situation) and schizophrenia treatments including adjunctive oral antipsychotics, other psychotropic drugs and non-pharmacological care.
- Functional remission at six months and its relationship to clinical remission were also analyzed

2.5. Patient population size

To measure the rate of functional remission at 12 months with a 95% confidence interval and 5% accuracy, we estimated that the analysis population size should be between 288 and 384 participants.

2.6. Statistics

Statistical analyses were performed with the SAS software (version 9.4, SAS Institute Inc., Cary, NC). Baseline demographic and clinical aspects of the study population were described as mean ± SD or % of patients. Clinical remission and functional remission rates were evaluated with a 95% confidence interval and their relationship was studied using a Chi-square test, the odds ratio (OD) and the attributable risk fraction (ARF).

Treatment persistence under baseline LAI was assessed and defined as the percentage of patients still treated with the same LAI at 12 months, with no switch during the study. The relationships between baseline characteristics and functional remission at twelve months were investigated using Chi-square test for categorical data and a Student's t-test or Mann–Whitney test for continuous data, depending on the normality of the distribution. No correction for multiple testing was applied in the univariate analysis identifying baseline variables possibly related to functional remission. Multiple logistic regression analysis was used to identify the best association of predictive factors explaining the functional remission at twelve months. The independent variables entering the model were chosen based on statistical considerations ($p < 0.20$ according to the univariate analysis) and clinical considerations. A stepwise procedure was used to select variables. Stepping was stopped when there were no further candidate variables that will enter the model at the 5% significance level. The results of the stepwise analysis were further confirmed by a multiple logistic regression analysis including all known or suspected variables (sociodemographic variables, PANSS-8 items scores; Birchwood items; treatments; data not shown).

3. Results

3.1. Patient disposition

A total of 364 patients were enrolled in the study (Fig. 1). 303 patients were included in the analysis and 61 patients were excluded (28 because of missing data and 33 because of major protocol deviations). The most frequent protocol deviations were: age >37 years ($n = 17$), patients without an acute episode within two months of inclusion ($n = 7$) and time from LAI initiation >103 days ($n = 4$). Among the 303 included patients, 29 patients discontinued the study (9.6%), 16 patients after inclusion and 13 patients after 6 months. Clinical and functional remission analyses were conducted on the sub-population of patients meeting the following criteria: good treatment adherence (>80%), appropriate time between visits, and assessments available for clinical and functional remissions (224 patients at 6 months and 228 patients at 12 months).

3.2. Baseline demographic and clinical aspects

Patients enrolled in the study were rather young, mostly men, and had a good level of education (half of them with high school or university degree) (Table 1). While most patients had an occupational activity before their illness, only one out of seven had a current occupation (Table 1). At baseline, 50 patients were under curatorship (Table 1), none under tutorship (exclusion criteria). The French individual protection legal system includes several measures, in which the two mains are the curatorship (the patient can receive assistance from a legally appointed person, but is free to decide by himself in his daily tasks), and the tutorship (most of decisions related to patient' life are taken by a guardian). Concerning family relationships, around 40% of patients were living alone and around 40% living with family (only 10.6% were living in a couple). Half of patients received parental

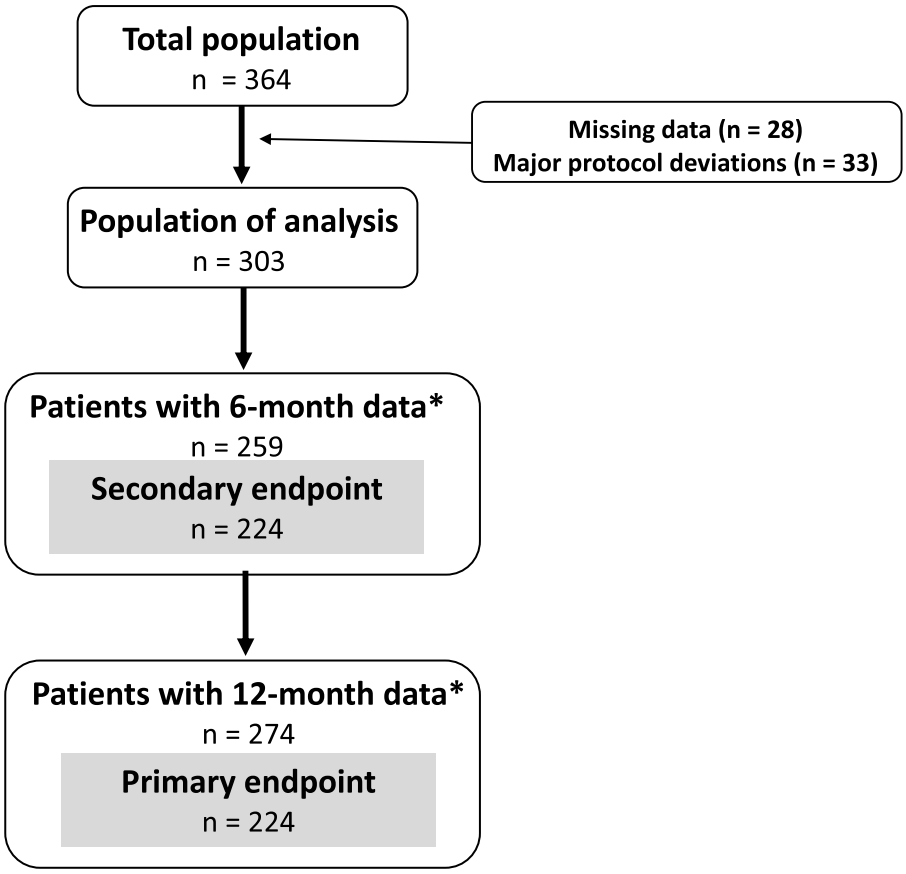

Fig. 1. Patient distribution. *Twenty-eight patients had data at 12 months, but they lacked data at 6 months. Clinical and functional remission analyses were conducted on a pre-defined sub-population of patients with treatment adherence >80%, appropriate time between visits, and assessments available for clinical and functional remissions at 12 months.

support (exclusively), and only a minority had no support from any relative. Among patients with existing support, 62.7% of them benefited from a permanent support, 34.1% received only sporadic support, and 3.1% faced hostile attitudes from their relatives (Table 1).

Regarding clinical and therapeutic aspects, the first episode of schizophrenia occurred at 21.6 years old on average, and an antipsychotic treatment was initiated in a short time period (23.1 years at mean) (Table 1). The mean duration of illness was 7.6 years (Table 1). Most patients (91.1%) initiated treatment with a second-generation LAI. 22.1% of patients received an oral adjunctive antipsychotic and 38.3% also received benzodiazepines. Moreover, more than half of the patients were receiving psychotherapy and one-third received psychosocial interventions.

Regarding patient clinical and functioning status at baseline, 15.2% of patients presented scores ≤3 on the 8 items of PANSS-8, and functional remission was already observed in 17.8% of patients (Table 2). The mean PSP baseline score was 51.1, and most patients had a good insight for the need of treatment as evaluated with the Birchwood scale (Table 2).

LAI treatment was initiated in study patients following an acute episode within the two months prior to participating in this study. Most patients included in the study received paliperidone LAI (45.5%) or aripiprazole LAI (28.4%) (Table 1).

The relationship between time under LAI treatment before inclusion and functional status at baseline was investigated. Functional scores were significantly higher in patients who had received LAI treatment for 45 days or more before inclusion compared to patient who had received LAI treatment for less than 45 days (FROGS total score: $p < 0.001$; PSP: total score $p < 0.05$; data not shown).

3.3. Functional and clinical remission

17.8% of patients were in functional remission at baseline (Table 2). This proportion then increased throughout the study to 37.1% at 6 months and 46.3% at 12 months (Fig. 2). 45.1% of patients were in clinical remission at 6 months and 55.1% at 12 months (Fig. 2). 39.8% of patients achieved both clinical and functional remission at 12 months.

At 6 and 12 months, the relationship between clinical and functional remission was highly significant ($p < 0.001$). At 12 months, 72.0% of patients who reached clinical remission also reached functional remission whereas only 14.9% of patients who had not reached functional remission (OR = 14.74 [7.52–28.90], $p < 0.0001$, $n = 226$; Fig. 2), corresponding to a high ARF of functional remission induced by clinical remission (AR = 79.37%).

The relationship between clinical and functional remission was further investigated in two subgroups. In patients with a duration of psychosis of more than five years, the relationship was confirmed (OR = 11.98 [5.20–27.62], $p < 0.0001$, $n = 138$), and was strengthened in patients with a duration of psychosis of less than five years (OR = 23.73 [6.84–82.36], $p < 0.0001$, $n = 80$).

Additionally, patients' FROGS and PSP scores increased during the study (Fig. 3A; normalized values, scale from 0 to 100) whereas patients' PANSS scores decreased for all 8 items throughout the study (Fig. 3B).

In the outcome analysis population, treatment persistence under LAI at baseline was 73.4% at 12 months.

3.4. Predictive factors of functional remission

Univariate analysis was used to study the patient's baseline characteristics as predictive factors of functional remission at 12 months (Fig. 4). Higher education ($p = 0.013$), current professional activity ($p = 0.013$) and good insight into the need for treatment ($p = 0.049$) were predictive factors of functional remission. In addition, the family environment was an important predictive factor, since the non-

Table 1
Baseline demographics and clinical characteristics.

Demographics	Total population
Number of patients	303
Age [years, mean (SD)]	29.3 (4.9)
<25 years, n (%)	63 (20.8%)
25–30 years, n (%)	83 (27.4%)
30–35 years, n (%)	110 (36.3%)
≥35 years, n (%)	47 (15.5%)
Gender [*n* (% male)]	223 (73.6%)
BMI [kg/m^2, mean (SD)]	25.3 (5.9)
Patients under curatorship [*n* (%)][a]	50 (16.5%)
Current family situation [*n* (%)]	
In family	133 (43.9%)
Alone	127 (41.9%)
In couple	32 (10.6%)
In institution	11 (3.6%)
Family relationships [*n* (%)]	
Only with parents	157 (51.8%)
With any relatives (sibling, partner, other +/− parents)	130 (42.9%)
None	16 (5.3%)
Type of existing relatives support [*n* (%)]	
Permanent	180 (62.7%)
Episodic	98 (34.1%)
Hostile attitude	9 (3.1%)
Education level [*n* (%)]	
Secondary school (no bachelor degree)	154 (51.9%)
High school degree	80 (26.9%)
University degree	63 (21.2%)
Occupational status [*n* (%)]	
Before illness	198 (67.1%)
Current situation	44 (14.5%)
Clinical characteristics	
Age of first psychotic episode [years, mean (SD)]	21.6 (4.5)
Duration of psychosis [years, mean (SD)]	7.6 (5.3)
<5 years	111 (37.8%)
5–10 years	75 (25.5%)
10–15 years	74 (25.2%)
≥15 years	34 (11.6%)
Age of first antipsychotic administration [years, mean (SD)]	23.1 (4.6)
History of psychiatric hospitalizations [*n* (%)]	293 (96.7%)
Type of LAI initiated [*n* (%)]	
Second generation[b]	276 (91.1%)
First generation[c]	27 (8.9%)
Adjunctive oral antipsychotic [n (%)][d]	67 (22.1%)
Other psychotropic treatments [n (%)]	
Benzodiazepines	116 (38.3%)
Other psychotropic treatment[e]	180 (59.4%)
Non-pharmacological support	
Psychotherapy	173 (57.3%)
Psychosocial care	113 (37.8%)

[a] The French individual protection legal system includes several measures, in which the two mains are the curatorship (the patient can receive assistance from a legally appointed person, but is free to decide by himself in his daily tasks), and the tutorship (most of decisions related to patient' life are taken by a guardian).

[b] Aripiprazole = 86 (28.4%), olanzapine palmitate = 20 (6.6%), risperidone microspheres = 32 (10.6%), paliperidone palmitate = 138 (45.5%).

[c] Zuclopenthixol decanoate = 7 (2.3%), flupentixol decanoate = 3 (1.0%), haloperidol decanoate = 17 (5.6%).

[d] Excepted same active molecule as LAI antipsychotic. [d]Anticholinergics = 66 (21.8%), anxiolytics = 67 (22.1%), hypnotics = 81 (26.7%), antidepressants = 38 (12.5%), other = 24 (7.9%).

[e] See text. BMI, body mass index. LAI, long-acting injectable antipsychotic.

exclusive support of parents (this means, parents together with siblings or other relatives) was a predictive factor of functional remission ($p = 0.003$). A lower severity of all PANSS-8 items at baseline was also a predictive factor of functional remission ($p < 0.05$).

The above univariate analyses were followed by a multivariate analysis which identified lower passive/apathetic behavior (social withdrawal N4 PANSS-8 item, $p < 0.0001$), good insight into the need for treatment (Birchwood's score $p = 0.020$), and non-exclusive parental support ($p = 0.004$) as predictors of functional remission at the 12-month of follow-up (Table 3).

Table 2
Baseline score values of PANSS, FROGS, PSP and Birchwood scales.

Number of patients	303
Baseline scores of PANSS-8 (each item: 1 to 7) [mean ± SD]	
Delusions	3.35 ± 1.50
Conceptual disorganization	3.31 ± 1.32
Hallucinations	2.63 ± 1.51
Mannerisms and posturing	2.61 ± 1.27
Unusual thought content	3.25 ± 1.28
Blunted affect	3.48 ± 1.32
Passive/apathetic social withdrawal	3.60 ± 1.34
Lack of spontaneity and flow of conversation	3.27 ± 1.35
Patients with scores ≤3 on the 8 items of PANSS-8 [n (%)]	46 (15.2%)
Baseline FROGS scores [mean ± SD]	
Social functioning dimension (11–55)	26.32 ± 7.61
Daily life dimension (4–20)	12.02 ± 3.09
Treatment dimension (4–20)	11.29 ± 3.39
Total score (19–95)	49.63 ± 12.63
Patients in functional remission[a] [n (%)]	54 (17.8%)
Baseline PSP score [mean ± SD]	51.1 ± 14.7
Patients with good insight on Birchwood scale [n (%)]	
Awareness of symptoms	110 (42.0%)
Awareness of illness	64 (24.2%)
Need for treatment	211 (82.1%)
Overall insight	79 (31.0%)

[a] Defined as a sub-score ≥33 on the first factor of the FROGS (social functioning) and sub-scores of ≥12 on the second (daily life) and third (health and treatment) factors (Gorwood et al., 2018). FROGS, Functional Remission of General Schizophrenia. PSP, Personal and Social Performance. PANSS, Positive and Negative Syndrome Scale.

4. Discussion

A good proportion of participants achieved functional remission after 12 months of treatment with LAI. Clinical remission was a main predictive factor for functional remission. Other predictive factors included the type of family environment, education level, status of employment, baseline functioning levels and patient level of insight.

The proportion of patients in functional remission increased throughout the study from 17.8% at baseline to 37.1% at 6 months and up to 46.3% at 12 months. As previously mentioned, patients could have been on LAI treatment for up to two months before inclusion and a longer time on treatment prior to baseline was related to higher functional scores at baseline, explaining the proportion of patients in functional remission at baseline (Table 2).

The proportion of patients in functional remission in this study (46.3%) compares well with values from previous studies investigating the effect of antipsychotic treatment on functional remission. Thus, Giraud-Baro et al. found that 42.1% of adult schizophrenia-spectrum chronic patients were in functional remission (evaluated with the GAF scale) after one-year LAI risperidone treatment (Giraud-Baro et al., 2016). Our study results also compare well with the reported 35% of never-treated patients that reached functional remission after antipsychotic treatment (oral or depot antipsychotics) for 3 years (Lambert et al., 2008), as well as with the 44% reported in first episode patients treated for 18 months (Conus et al., 2017), and with the 44.5% of adult patients with chronic schizophrenia evaluated using the FROGS scale in the European Group On Functional Outcomes and Remission in Schizophrenia study (EGOFORS) (Gorwood et al., 2018). However, it is higher than the reported 26.6% of patients that received atypical or conventional antipsychotics for 2 years (Lambert et al., 2006), as well as with the 32.1% of patients in psychosocial remission that were treated with antipsychotics for at least 6 months (Valencia et al., 2015) and with the 25.4% of outpatients with schizophrenia followed for 2 years (Haro et al., 2011). Until now, functional remission studies have used different scales and evaluated heterogeneous populations (for critical review, see Brissos et al., 2014) and, to the best of our

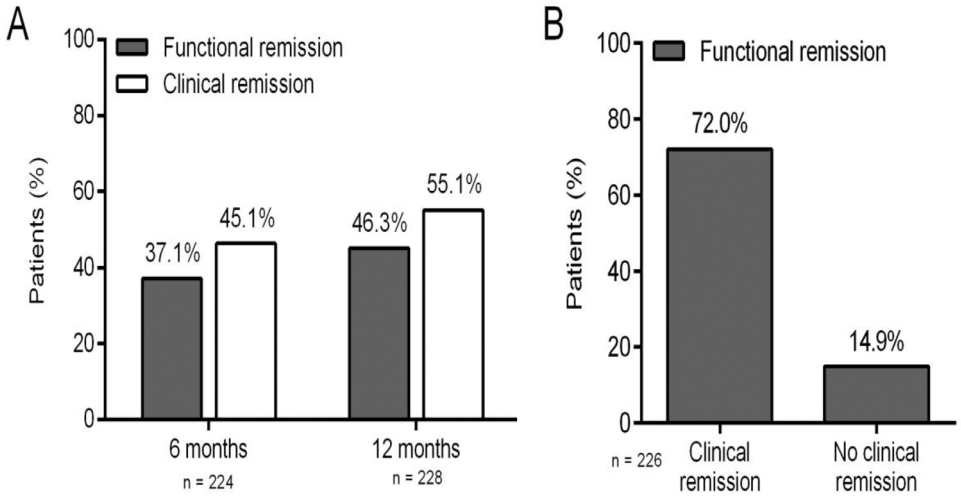

Fig. 2. Functional and clinical remission. A. Functional and clinical remission at 6 and 12 months. B. The relationship between clinical remission and functional remission at 12 months.

knowledge, no study has compared functional remission rates with LAI versus oral formulations. Additional research comparing LAI and oral treatments is needed to assess their respective interest for functional remission and support clinical decision making.

More than half of patients reached clinical remission in this study. This rate is similar to the 58.4% of patients in clinical remission (mild intensity in core psychotic symptoms of the PANSS) reported by Giraud-Baro et al. (2016) after 12 months of LAI risperidone treatment, but higher than the 39.3% of patients treated with oral quetiapine (Smeraldi et al., 2013). Moreover, Levine et al. (2011) also found low levels of clinical remission in patients that were treated with oral antipsychotics (between 6.3 % for risperidone and 12.4 % for olanzapine). These differences could be explained by intrinsic properties of LAI, increasing the likelihood of treatment adherence (Leucht et al., 2011) and favoring more stable plasmatic concentrations as compared to oral treatments (Mallikaarjun et al., 2013).

39.8% of patients achieved both clinical and functional remission at 12 months. This compares well with previous studies showing functional remission in about one-third of treated patients reaching symptomatic remission (Bobes et al., 2009; Lambert et al., 2006; San et al., 2007; Wunderink et al., 2009). A strong relationship between functional and clinical remission in early-to-mid-stage patients treated with LAI was found in this study. These results are similar to those previously obtained in another cohort using the FROGS scale (Gorwood et al., 2018), in which functional remission was also reached in 65.2% of patients that reached clinical remission, whereas only 13.5% of patients reached functional remission without clinical remission.

Interestingly, early-stage patients (less than five years of psychosis duration) were twice as likely to reach functional remission when clinical remission was obtained than mid-stage patients (more than five

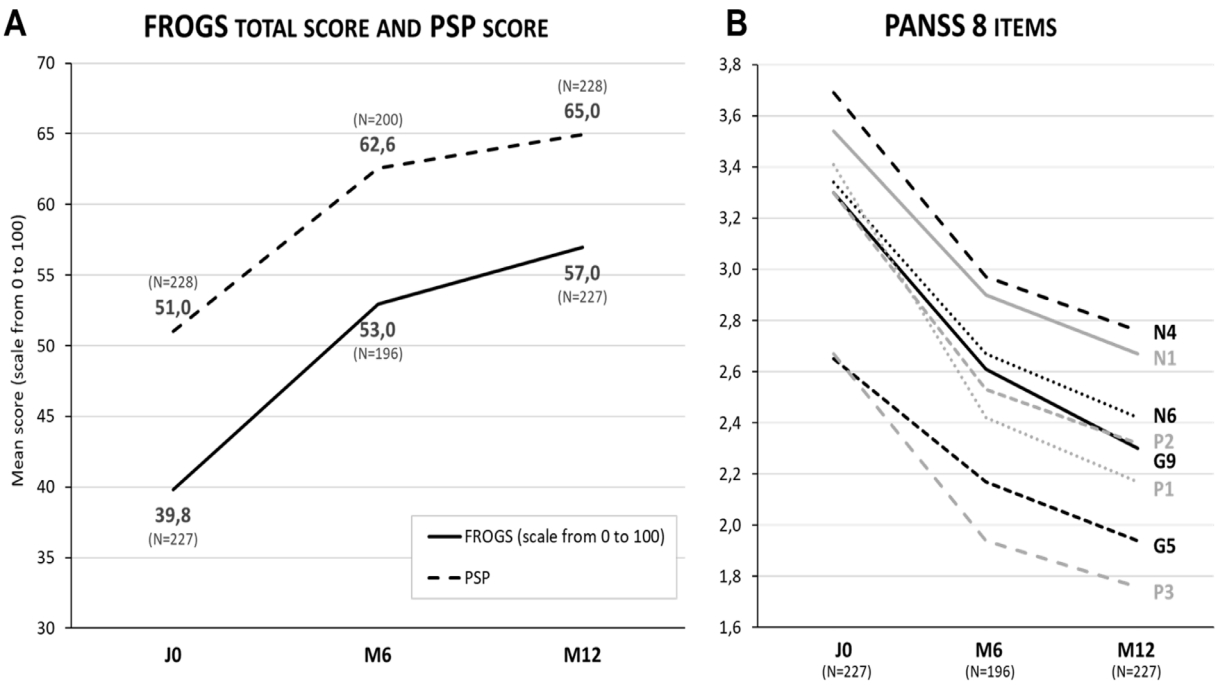

Fig. 3. The evolution of functional and clinical scores throughout the study. A. Evolution of PSP and FROGS total scores during the study (normalized values, scales from 0 to 100). B. Evolution of PANSS-8 items scores during the study. FROGS, Functional Remission of General Schizophrenia. PSP, Personal and Social Performance. PANSS, Positive and Negative Syndrome Scale. P, N and G indicate positive, negative and general psychopathologic symptoms, respectively.

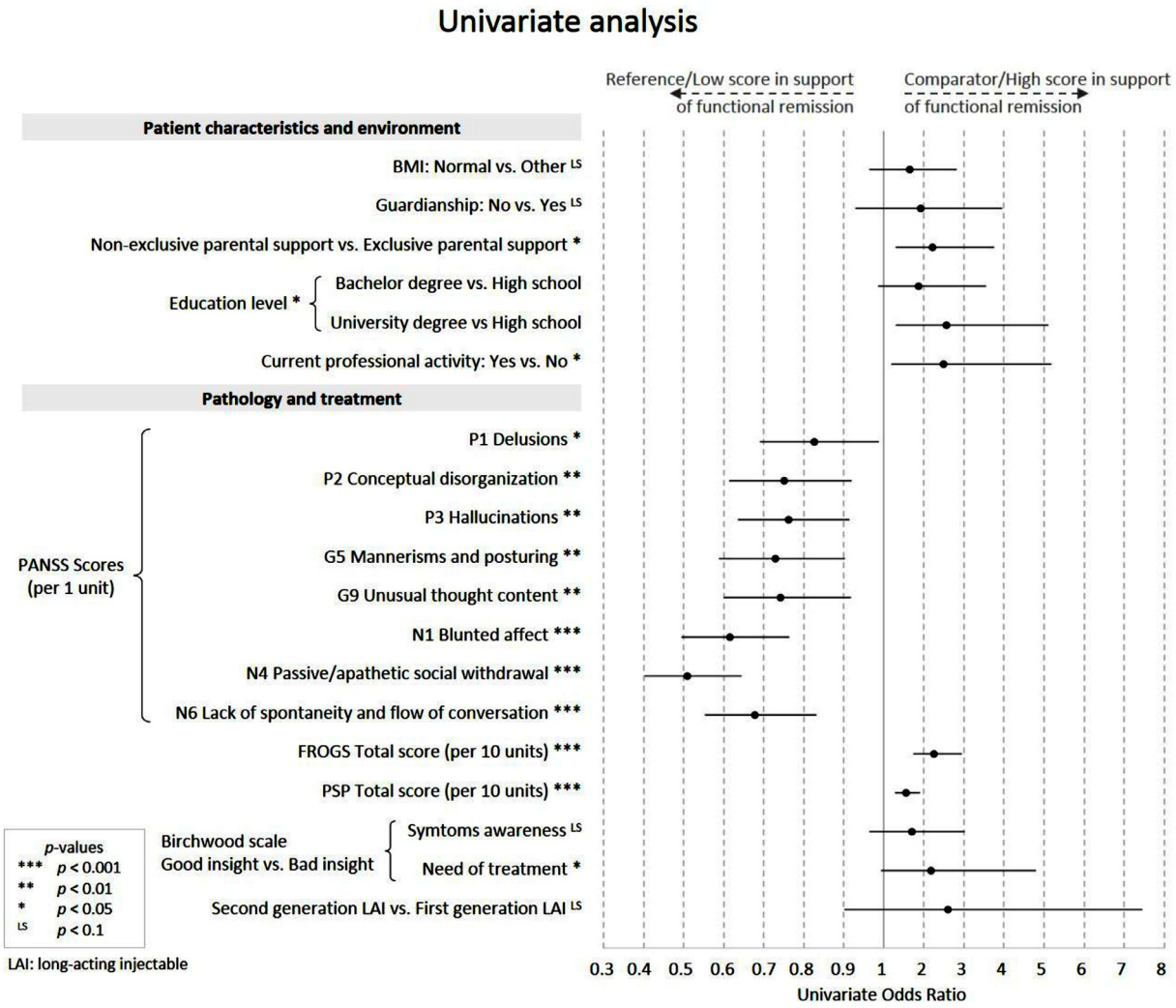

Fig. 4. Identification of baseline characteristics predictive of functional remission at 12 months. Univariate analyses are presented as odd ratios. Categorical variables are presented as Comparator vs Reference (for example: BMI: Normal (comparator) vs Other (reference)). Odd ratios > 1 indicate that a high score (continuous variables) or comparator (categorical variables) at baseline is predictive of functional remission at 12 months (for example, having a high FROGS total score or non-exclusive parental support (comparator) at baseline is predictive of functional remission at 12 months). Conversely, odd ratios < 1 indicate that a low score at baseline is predictive of functional remission at 12 months (for example, a low N4 PANSS score at baseline is predictive of functional remission at 12 months). P-values were calculated using a chi-square test for categorical data and Student's *t*-test or Mann–Whitney test for continuous data depending on normality. BMI, Body Mass Index. PANSS, Positive and Negative Syndrome Scale. P, N and G indicate positive, negative and general psychopathologic symptoms, respectively.

Table 3
Multivariate analysis of functional remission predictors at 12 months of follow-up.

Variable	Odds ratio (95% CI)	*p*-value*
Passive/apathetic, social withdrawal (PANSS-8)	0.49 (0.38–0.64)	<0.0001
Patient relatives		
Non-exclusive parental support	2.56 (1.34–4.89)	0.0043
Good insight into need for treatment (Birchwood score)	2.31 (1.14–4.69)	0.0203

* Wald Chi-square test. CI, confidence interval. LAI, long-acting injectable, PANSS, Positive and Negative Syndrome Scale.

years of psychosis duration). This result emphasizes the need to focus on early intervention programs in order to maximize the possibility of recovery in schizophrenia. Furthermore, the fact that approximately 80% of functional remission is attributable to clinical remission favors the importance of interventions targeting clinical symptoms, aside from the interventions devoted to functionality.

Moreover, results confirmed low levels of negative symptoms as important predictive factors of functional remission (Albert et al., 2011, Austin et al., 2013; Jordan et al., 2014; Lysaker and Davis, 2004; Milev et al., 2005; Robinson et al., 2004; Schennach-Wolff et al., 2009; Spellmann et al., 2012; Valencia et al., 2015) and showed that reduced positive and negative clinical symptoms are predictive of functional remission. Current treatment of negative symptoms of schizophrenia remains a great unmet need (Garay et al., 2016), and some therapeutic options have recently demonstrated efficacy in reducing the PANSS negative factor score (Davidson et al., 2017; Nemeth et al., 2017). Therefore, it would be interesting to evaluate whether adding such treatments could increase functional remission rates with LAI.

Other predictive factors, such as education level, employment status, and patient quality of insight (insight into the need for treatment), are key factors for functional remission (Alenius et al., 2010; Chan et al., 2018), highlighting the importance enhancing initiatives that favor occupational activities, training and insight improvement. Patient perception is a key factor in the treatment of schizophrenia (Lysaker et al., 2018). Various approaches, including psychotherapy (Yilmaz and Okanli, 2018), atypical antipsychotics (Mattila et al., 2017) and transcranial direct current stimulation (Chang et al., 2018) have

been shown to improve insight in schizophrenia. Adjunctive therapy aiming at insight improvement could be of interest in reaching functional remission (Yilmaz and Okanli, 2018).

Surprisingly, having non-exclusive parental support (such as having siblings in addition to parents) is also a predictor of functional remission. To our knowledge, this is a new predictor of functional remission and complements an observation that remission from first-episode psychosis is associated with growing up with both parents (Albert et al., 2011). These results suggest that being supported by different or additional family members favors functional remission and highlights the role of close relatives in patient-related outcomes.

Future research is needed to reach consensus on the concept and measures of functional remission and further demonstrate the FROGS remission threshold as an accurate measure of functional remission in patients with schizophrenia (Gorwood et al., 2018). Moreover, a 4 items-only version of the FROGS scale has been recently validated and may be useful to assess functional remission in clinical practice (Mallet et al., 2018).

4.1. Limitations

Clinical and functional remission analyses were conducted on a predefined sub-population of patients with treatment adherence > 80%, appropriate time between visits, and assessments available for clinical and functional remissions at 12 months. Therefore, outcome analyses were conducted on a population of 228 patients at 12 months, with a precision of 7% instead of 5%. Furthermore, only patients without guardianship or under curatorship were included in this study, patients under tutorship were excluded and may have influenced the study patient profile.

4.2. Conclusions

In summary, almost half of the patients treated with LAI achieved functional remission in this study. Improvement of clinical status is closely related and largely contributes to functional remission, especially so in the early period of the disorder, stressing the key role of continuous and appropriate symptomatic treatment of early-to-mid-stage schizophrenic patients to reach functional remission and maximize their chances of recovery. Finally, non-exclusive parental support was found to be an important predictor of functional remission in an early-to-mid-stage LAI population strengthening the role and influence of close relatives in patient-related outcomes. These findings complement previous studies showing that functional and clinical remission can be achieved and should be considered as a treatment goal in patients with schizophrenia.

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CRediT authorship contribution statement

Philip Gorwood: Methodology, Writing - original draft, Writing - review & editing. **Sophie Bouju:** Methodology, Writing - original draft, Writing - review & editing. **Cécile Deal:** Formal analysis, Writing - original draft, Writing - review & editing. **Charlotte Gary:** Writing - original draft, Writing - review & editing. **Catherine Delva:** Writing - original draft, Writing - review & editing. **Sylvie Lancrenon:** Formal analysis, Writing - original draft, Writing - review & editing. **Pierre-Michel Llorca:** Methodology, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

Sophie Bouju, Cécile Deal and Charlotte Gary are employees at Janssen Cilag (Issy-les-Moulineaux, France). During the last five years, Philip Gorwood received research grants from Eli Lilly, Ethypharm and Servier, as well as fees for presentations at congresses or participation in scientific boards from Alcediag-Alcen, AstraZeneca, Bristol-Myers-Squibb, Janssen, Lilly, Lundbeck, Otsuka and Servier. During the last 5 years, Pierre-Michel Llorca received research grants, as well as fees for presentations at congresses or participation in scientific boards from Allergan, Gedeon-Richter, Gilead, Janssen, Lilly, Lundbeck, Otsuka, Recordati, Sanofi, Takeda, and Teva. Sylvie Lancrenon and Catherine Delva have no conflict of interest to declare.

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Supplementary materials

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