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Original article

Changes in attitude towards LAI antipsychotic maintenance treatment: A two-year follow-up study

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ABSTRACT

Background: To present real-world evidence on the effects of switching from oral to long-acting injectable (LAI) antipsychotic maintenance treatment (AMT) in a sample of clinically stable patients with schizophrenia, with regard to subjective experience of treatment, attitude towards drug and quality of life.

Methods: 50 clinically stable adult schizophrenic outpatients were recruited. At the time of enrolment (T0), all patients were under a stabilized therapy with a single oral second-generation antipsychotic (SGA) and were switched to the equivalent maintenance regimen with the long-acting formulation of the same antipsychotic. 43 patients completed the 24-month prospective, longitudinal, open-label, observational study. Participants were assessed at baseline (T0), after 12 (T1) and 24 months (T2), using psychometric scales (PANSS, YMRS and MDRS) and patient-reported outcome measures (SWN-K, DAI-10 and SF-36).

Results: The switch to LAI-AMT was associated with a significant clinical improvement at T1 and T2 compared to baseline (T0). All of the psychometric indexes, as well as patients' subjective experience of treatment (SWN-K), and quality of life (SF-36) showed a significant improvement after one year of LAI-AMT, with stable results after two years. Patients' attitude towards drug (DAI-10) increased throughout the follow-up period, with a further improvement during the second year.

Conclusions: The switch to LAI-AMT may help to address the subjective core of an optimal recovery in stabilized schizophrenic patients. A sustained improvement in patients' attitude towards drug may help to achieve patient's compliance. The size of this study needs to be expanded to produce more solid and generalizable results.

1. Introduction

Schizophrenia is a heterogeneous and chronic syndrome associated with a severe impairment of personal and social functioning [1,2]. Since relapse is associated with illness progression and resistance to therapy, the importance of antipsychotic maintenance treatment (AMT) is clearly established [3,4]. Nonetheless, non-adherence is common in psychotic disorders and represents a major determinant of relapse and hospitalization, thus leading to a poor prognosis [5,6]. Long-acting injectable antipsychotics (LAIs) are described as an increasingly valuable option to improve compliance and a wide range of other clinical and social outcomes, including reduced healthcare costs [7–12]. In fact, when compared to oral AMT, LAIs proved to be associated with a considerable reduction in relapse and readmission risk in mirror and cohort studies [13–15]. Although such difference was not consistently reported by randomized-controlled trials, this research design was claimed to not adequately address real-world practice [15,16].

On the other side, the ongoing debate on AMT seems to neglect, at least in part, patient-reported outcomes (PROs), which have

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been previously described in terms of adverse subjective experiences, tolerability and quality of life associated with AMT [17–19]. Nevertheless, perceived well-being under antipsychotics is relevant to compliance [20,21], and should be regarded as an outcome of interest in a recovery-oriented clinical approach [22].

Although increasing evidence indicates the protective value of positive attitudes towards treatment and subjective well-being against relapse and readmission risk [5,6,17,20,21], real-world clinical research on subjective outcomes of LAI antipsychotics use, focusing on patient's perspective, is still scarce. Such lack of a systematic assessment of patient's subjective experience with adequate patient-reported measures in long-term observational studies may account for the minimal advancement of research on this topic [18,19,23]. Available evidence on subjective experience of AMT mainly relies on studies on oral therapy and underlines a better tolerability of second-generation antipsychotics (SGA) over first-generation antipsychotics (FGA) [18]. Moreover, SGA-LAIs seem to be associated with better subjective experience compared to first-generation depot formulations [24,25]. Although patients' attitude towards LAIs before their use is often influenced by negative beliefs about this formulation [26–28], only a few studies evaluated the impact of switching to a SGA-LAI on PROs [29–36]. In this regard, our LAI-FE study (LAIs on Functioning and Experience), ongoing at the University of Florence, provided some evidence of an improved subjective experience with SGA-LAIs in the short-term [35,36]. Such lower propensity of LAI antipsychotic formulations to cause adverse subjective experiences could be due to their peculiar pharmacokinetic and pharmacodynamic characteristics (they allow to control titration to effective dose, to steady plasma drug levels, to avoid first-pass metabolism and to guarantee delivery of medication [7,8]), as well as to other individual and environmental treatment-related factors (i.e. not having to take pills may increase social adaptation, autonomy, and may reduce stigma; periodic treatment monitoring may improve therapeutic alliance, etc.) [5,6].

In particular, in our previous mirror [35] and case-control [36] studies, we found significant improvements of patients' attitude towards treatment after 6-month of LAI antipsychotic treatment. At the same time, during the LAI-FE study, we recognized the importance of investigating the subjective experience of AMT over longer periods of time, in order to address different real-world situations.

For this reason, in the present study, we aimed at evaluating long-term PROs after switching AMT from an oral SGA to the corresponding LAI formulation. A mirror-design was chosen to address schizophrenic patients' experience in terms of subjective well-being, attitude towards treatment and quality of life. A 24-month follow-up was set in order to minimize the impact of a possible expectancy bias. To our knowledge, no study has yet targeted such a comprehensive group of PROs in a two-year trial.

2. Methods

2.1. Study design

This 24-month, prospective, longitudinal, open-label, non-randomized, single-arm, observational study is part of the wider LAI-FE observational project currently ongoing at the LAI clinic of the the Psychiatric Unit of the Department of Health Sciences of the University of Florence (Italy). The present study comprises three parts: a baseline visit (T0), and two prospective follow-up visits at month 12 (T1) and month 24 (T2). The study was purely observational and in no way influenced the intervention that patients would have received otherwise. The whole project is conducted in accordance with the current International Conference on Harmonisation of Technical Requirements for Good Clinical Practice guidelines, as contained in the Declaration of Helsinki. The study protocol and consent were approved by the Independent Ethics Committee of the study centre. All of the diagnostic procedures and psychometric tests are part of the routine clinical assessment performed at our clinic. The project protocol was fully explained and all patients provided written consent to the collection and analysis of their data. Patient confidentiality was ensured at all times.

2.2. Participants

All adult outpatients with schizophrenia [37,38] attending our LAI clinic between July 2015 and January 2016 and who required a long-term antipsychotic treatment were consecutively enrolled in the study, provided they met the following inclusion criteria:

a) age between 18 and 65 years,
b) had been clinically stable on a stabilized single oral AMT with either olanzapine, paliperidone or aripiprazole for more than 4 weeks,
c) were about to be switched to the equivalent maintenance regimen with the LAI formulation of the same antipsychotic (olanzapine pamoate [39], paliperidone palmitate [40] or aripiprazole monohydrate [41]), according to current clinical guidelines [42] suggesting that LAIs should be systematically considered and proposed to any patient for whom AMT is indicated.

Clinical stability was defined by means of the Positive And Negative Syndrome Scale (PANSS) [43], the Montgomery-Asberg Depression Rating Scale (MADRS) [44], and the Young Mania Rating Scale (YMRS) [45], as having all of the following:

- outpatient status,
- PANSS total score $\leq$ 120 (not severely ill) [46],
- MADRS total score < 30 (not severely ill) [47],
- YMRS total score < 25 (not severely ill) [48],
- A score of $\leq$ 4 on each of the following PANSS items: delusions (P1), conceptual disorganization (P2), suspiciousness (P3), hallucinatory behaviour (P6), unusual thought content (G9),
- A score of $\leq$ 2 on item 10 of the MADRS ("Weary of life. Only fleeting suicidal thoughts").

Moreover, in the clinicians' judgment, enrolled patients were expected to follow the new intervention and not to need significant changes in concomitant pharmacological or non-pharmacological treatments during the follow-up. They were also expected to regularly attend the psychiatric consultations coordinated with the dates of the injections.

Patients were excluded if they had been treated with clozapine during the previous 3 months or had previously demonstrated poor response or tolerability to any LAI antipsychotic. Patients were also excluded if they had: current diagnosis of other psychiatric and/or substance use disorders, serious and unstable medical condition, neurological and/or cognitive impairment or illiteracy, history or current symptoms of tardive dyskinesia, history of severe drug allergy or hypersensitivity, history of neuroleptic malignant syndrome. Female patients who were pregnant, breastfeeding or without adequate contraception were also excluded.

After applying the mentioned inclusion and exclusion criteria, 50 patients with schizophrenia were enrolled. As previously said, five patients failed to complete the study protocol, so that the final sample therefore consisted of 43 patients (26 males and 17 females). All patients received monthly psychiatric consultations for the whole duration of the study. Since the outpatient service of our LAI clinic belongs to the National Health System and guarantees full accessibility to general population, needed treatments were provided at no cost for patients.

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2.3. Assessment

Patients were assessed at enrolment (baseline visit before the switch at T0), and after 12 (T1) and 24 (T2) months of LAI antipsychotic treatment (prospective follow-up visits). Socio-demographic, clinical and treatment data were collected at each visit by expert psychiatrists who had no therapeutic relationship with any of the participants they assessed.

Diagnosis of schizophrenia was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [37] as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders - Patient edition (SCID-I/P) [38], and confirmed by treating clinician for compatibility between old DSM-IV-TR [49] and new DSM-5 diagnostic criteria.

Symptomatic improvement of enrolled patients was measured by evaluating the changes in the PANSS, the MADRS and the YMRS mean scores between follow-up visits.

2.4. Outcome measures

Together with the mentioned psychometric assessment of changes in psychopathology, the following PROs were assessed:

a) attitude towards treatment, as measured by the Drug Attitude Inventory short version (DAI-10) [50];
b) subjective experience of treatment, as measured by the Subjective Well-Being Under Neuroleptics scale short form (SWN-K) [51];
c) health-related quality of life, as measured by the Short Form-36 health survey (SF-36) [52,53].

The DAI-10 [50] is a 10-item self-rating scale, developed to assesses how the attitude, experience and beliefs of patient about antipsychotics may affect compliance. Scores range from -10 (very poor attitude) to +10 (best possible attitude).

The SWN-K [51] is a 20-item self-rating scale, developed to measure the subjective experience of psychotic patients associated with the use of antipsychotics. It contains five subscales consisting of four items each: mental functioning, self-control, emotional regulation, social integration and physical functioning. The total score ranges from a minimum of 20 (poor subjective experience) to a maximum of 120 (excellent subjective experience).

The SF-36 [52,53] is a 36-question, self-reported measure of quality of life, generating scores for eight domains: general health, vitality, role emotional (ability to perform life role based on emotional functioning), mental health (depression and anxiety), physical functioning (ability to perform physical tasks), role physical (ability to perform life role, i.e. work based on physical functioning), bodily pain and social functioning (ability to perform social tasks). Each scale is linearly transformed into a 0-to-100 scale with higher scores representing better health status and functioning. The survey also includes a single item that provides an indication of perceived change in health.

2.5. Statistical analysis

For discrete variables, absolute and relative frequencies were calculated, and Pearson's chi-square test (χ^2) was performed when appropriate. For continuous variables, descriptive statistics (mean ± standard deviation [SD], mean ± standard error [SE], median, range) were calculated. Paired samples Student's *t*-test was performed when appropriate for repeated measures analysis. Statistical analysis was performed by means of the Statistical Package for Social Sciences (SPSS) for Windows (release 21.0, IBM, 2012).

3. Results

3.1. Patients and treatment

A total of 50 patients with schizophrenia were enrolled in the present study. As said, all of the patients were switched to the LAI formulation of the previous oral antipsychotic according to current clinical guidelines suggesting that LAIs should be systematically considered and proposed to any patient for whom AMT is indicated [42]. However, five patients failed to complete the study protocol because they moved to another region and therefore decided to continue their LAI treatment program in a different outpatient facility of the National Health Service. Moreover, two patients required a change in antipsychotic treatment during the first six months of follow-up due to the late onset of clinically relevant treatment-emergent adverse events (weight gain with olanzapine and symptomatic hyperprolactinemia with paliperidone).

The final sample of this study therefore consisted of 43 Caucasian patients with schizophrenia, 26 males (60.5%) and 17 females (39.5%). The mean age of the sample was 38.44 ± 11.10 years and the mean level of education was 12.44 ± 3.72 years of study. Most patients were single or not in a stable relationship (69.8%). As for the clinical history, the study sample had a mean of 17.81 ± 11.39 years of illness duration, 3.93 ± 2.58 episodes of illness, 2.86 ± 1.57 different antipsychotics received in the past, and 3.23 ± 2.29 hospitalizations.

Clinical and treatment characteristics of the final sample are summarized in Table 1. The study sample included 2 patients treated with oral aripiprazole (30 mg/day), 28 with oral olanzapine (10–15 mg/day), and 13 with oral paliperidone (9–12 mg/day), who were switched to the equivalent regimen with LAI aripiprazole monohydrate (400 mg/month), LAI olanzapine pamoate (300–405 mg/month), and LAI paliperidone palmitate (100–150 mg/month) respectively. No clinically significant treatment-associated adverse events (TAEs), post-injection syndrome (PIS) reactions, side effects or local complications in the site of injections occurred during the whole duration of the study. All patients regularly attended the monthly follow-up psychiatric consultations, which were coordinated with the dates of the injection. Concomitant medications were recorded throughout the study: the rates of change in concomitant treatments did not vary significantly during follow-up (Table 1).

3.2. Efficacy measures

Repeated measures analysis showed a significant improvement of all of the psychometric indexes between T0 and T1, and between T0 and T2, with no significant difference between T1 and T2 (Table 1). More in details, both the T0-T1 and the T0-T2 comparisons found highly significant reductions in mean PANSS total score ($t_{T0\text{-}T1} = 5.30$, $p < .001$, $t_{T0\text{-}T2} = 5.66$, $p < .001$), YMRS ($t_{T0\text{-}T1} = 5.36$, $p < .001$, $t_{T0\text{-}T2} = 5.95$, $p < .001$) and MDRS ($t_{T0\text{-}T1} = 5.82$, $p < .001$, $t_{T0\text{-}T2} = 4.55$, $p < .001$). All mean PANSS subscale scores showed statistically significant changes in both T0-T1 and T0-T2 comparisons with regard to general ($t_{T0\text{-}T1} = 5.23$, $p < .001$, $t_{T0\text{-}T2} = 5.77$, $p < .001$), positive ($t_{T0\text{-}T1} = 5.65$, $p < .001$, $t_{T0\text{-}T2} = 5.89$, $p < .001$) and negative symptoms ($t_{T0\text{-}T1} = 3.74$, $p = .001$, $t_{T0\text{-}T2} = 3.75$, $p = .001$). No significant difference in mean PANSS subscale scores was found between T1 and T2 (Table 1).

3.3. Patient-reported outcomes

In this study, patients reported a highly significant progress in their subjective experience of treatment between T0 and T1, and between T0 and T2, with a statistically significant improvement of all of the five SWN-K subscale mean scores

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Table 1
Clinical and treatment characteristics of the sample.

	AMT				χ^2 or t (T0-T1)	χ^2 or t (T1-T2)	χ^2 or t (T0-T2)	p (T0-T1)	p (T1-T2)	p (T0-T2)
	T0 N=43	T1 N=43	T2 N=43							
Psychopathology										
PANSS	75.40 ±39.58		55.70 ±33.91	54.12 ±28.77	5.30	0.56	5.66	**.000**	.758	**.000**
General	39.47 ±19.11		28.37 ±14.56	28.40 ±14.51	5.23	-.08	5.77	**.000**	.934	**.000**
Positive	18.37 ±11.18		11.35 ±7.27	11.14 ±7.04	5.65	.35	5.89	**.000**	.730	**.000**
Negative	17.72 ±11.43		14.26 ±9.14	14.07 ±9.44	3.74	.22	3.75	**.001**	.826	**.001**
YMRS	8.65 ±8.22		2.98 ±5.05	2.63 ±4.11	5.36	.72	5.95	**.000**	.479	**.000**
MDRS	16.05 ±7.55		9.19 ±7.94	9.40 ±8.45	5.82	-.18	4.55	**.000**	.860	**.000**
LAI antypsychotic treatment										
Aripiprazole	400 mg/month	2 (4.7)	2 (4.7)	2 (4.7)	.000	.000	.000	1.00	1.00	1.00
Olanzapine	300 mg/month	4 (9.3)	4 (9.3)	4 (9.3)	.000	.000	.000	1.00	1.00	1.00
	405 mg/month	24 (55.8)	24 (55.8)	24 (55.8)	.000	.000	.000	1.00	1.00	1.00
Paliperidone	100 mg/month	5 (11.6)	5 (11.6)	5 (11.6)	.000	.000	.000	1.00	1.00	1.00
	150 mg/month	8 (18.6)	8 (18.6)	8 (18.6)	.000	.000	.000	1.00	1.00	1.00
Change in concomitant treatments in the previous year										
Antidepressant	Start	8 (18.6)	7 (16.3)	7 (16.3)	1.91	1.63	.548	.315	.577	.597
	Stop	5 (11.6)	4 (9.3)	4 (9.3)	.580	.452	.580	.446	1.00	.446
Mood stabilizer	Start	2 (4.7)	1 (2.3)	1 (2.3)	.050	.024	.050	.823	.876	.823
	Stop	4 (9.3)	5 (11.6)	3 (7.0)	.580	.424	.331	.446	.515	.565
Anxiolytic	Start	4 (9.3)	2 (4.7)	5 (11.6)	.215	.276	.580	.643	.599	.446
	Stop	3 (7.0)	6 (14.0)	1 (2.3)	.523	.166	.077	.470	.684	.782

Table legend. *Statistics*: Discrete variables are reported as number (within-group percentage); Continuous variables are reported as mean ± standard deviation. *Abbreviations*: AMT, Antipsychotic Maintenance Treatment; N, number; PANSS, Positive and Negative Syndrome Scale total score; General, general psychopathology subscale of the PANSS; Positive, positive subscale of the PANSS; Negative, negative subscale of the PANSS; YMRS, Young Mania Rating Scale; MDRS, Montgomery-Asberg Depression Rating Scale; LAI, Long-acting injectable; DAI-10, Drug Attitude Inventory short version.

in both comparisons ($p < .001$) (Fig. 1). More in details, significant improvements were detected in emotional regulation ($t_{T0\text{-}T1} = -4.72$, $p < .001$, $t_{T0\text{-}T2} = -3.98$, $p < .001$), self-control ($t_{T0\text{-}T1} = -6.40$, $p < .001$, $t_{T0\text{-}T2} = -5.71$, $p < .001$), mental functioning ($t_{T0\text{-}T1} = -4.89$, $p < .001$, $t_{T0\text{-}T2} = -4.33$, $p < .001$), physical functioning ($t_{T0\text{-}T1} = -5.58$, $p < .001$, $t_{T0\text{-}T2} = -4.49$, $p < .001$) and social integration ($t_{T0\text{-}T1} = -5.14$, $p < .001$, $t_{T0\text{-}T2} = -4.25$, $p < .001$). No significant changes were observed between T1 and T2 in any of the mean SWN-K subscale scores (Fig. 1).

A significant increase of mean DAI-10 total score was found both in the first ($t_{T0\text{-}T1} = -6.48$, $p < .001$) and in the second ($t_{T1\text{-}T2} = -2.19$, $p = .034$) follow-up period, with a remarkable increase of overall patient's attitude towards LAI-AMT during the two-year follow-up ($t_{T0\text{-}T2} = -7.27$, $p < .001$) (Fig. 2).

A generalized expansion of health-related quality of life (as measured by the SF-36) was observed for all the areas of daily living between T0 and T1 and between T0 and T2, although with different levels of statistical significance (Fig. 3). In fact, patients reported a

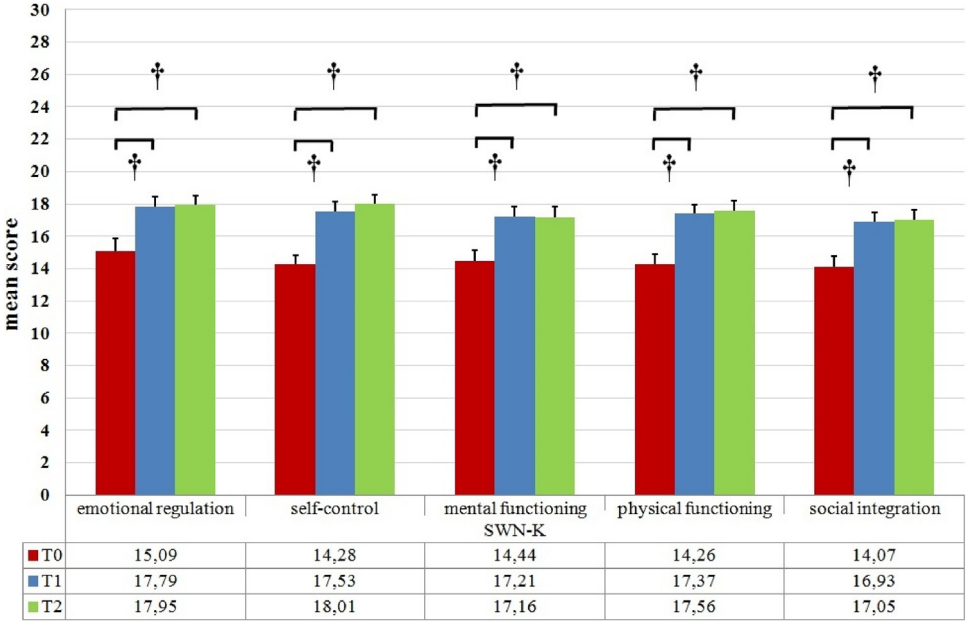

Fig. 1. Subjective experience of treatment at baseline and after twelve and twenty-four months of LAI antipsychotic maintenance treatment.
Statistics: †, $p < .001$. *Abbreviations:* SWN-K, SubjectiveWell-Being Under Neuroleptics scale short form; T0, baseline visit ; T1, 12-month follow-up visit; T2,24-month follow-up visit.

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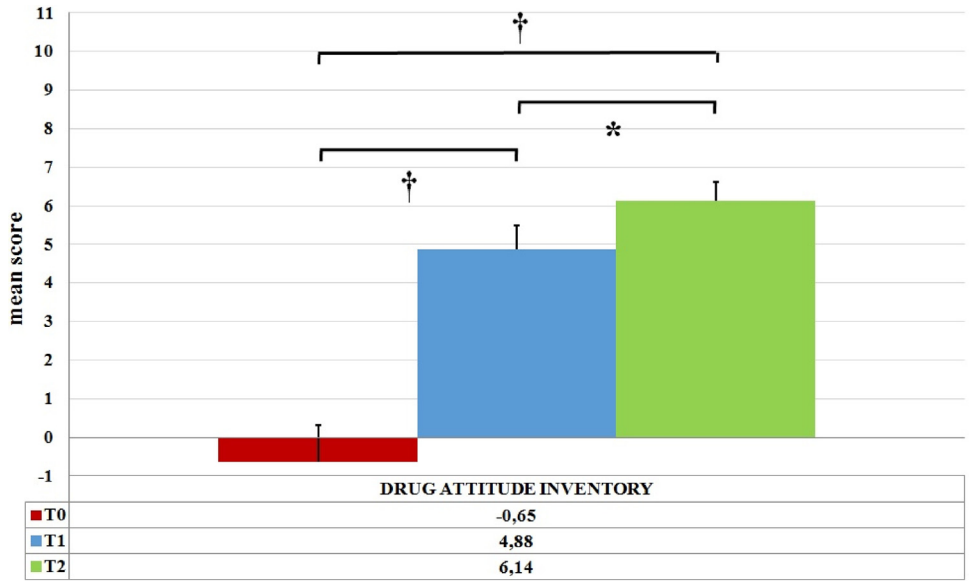

Fig. 2. Attitude towards treatment at baseline and after twelve and twenty-four months of LAI antipsychotic maintenance treatment.
Statistics: *, p < .05; †, p < .001. *Abbreviations:* T0, baseline visit ; T1,12-month follow-up visit; T2, 24-month follow-up visit.

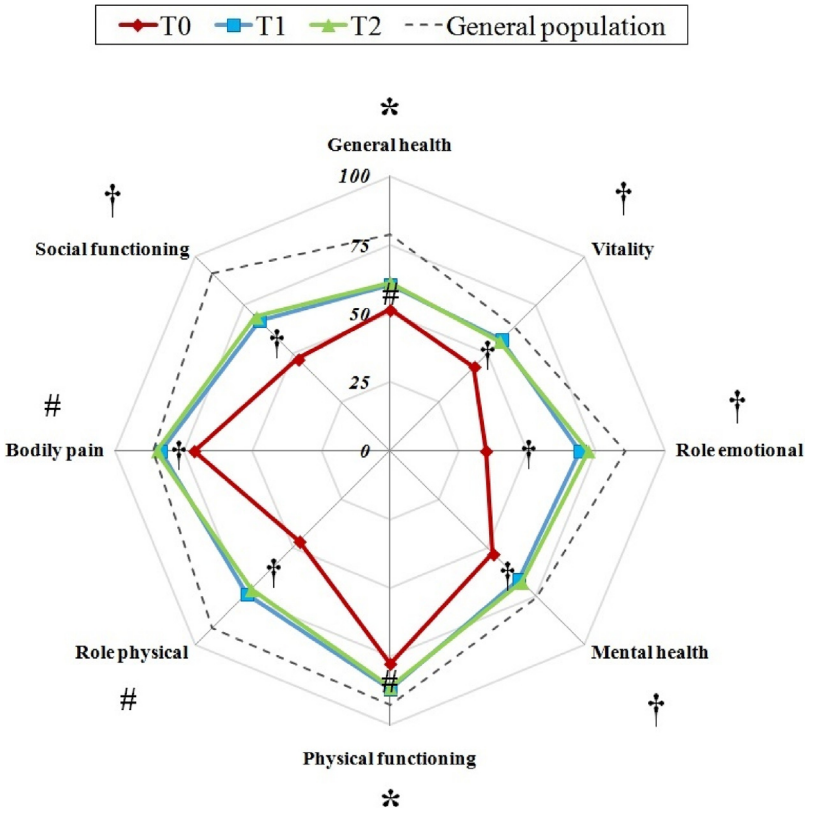

Fig. 3. Health-related quality of life at baseline and after twelve and twenty-four months of LAI antipsychotic maintenance treatment.
Statistics: *, p < .05; #, p < .01; †, p < .001. Mean scores are presented on a 0-to-100 scale. *Abbreviations*: T0, baseline visit; T1,12-month follow-up visit; T2, 24-month follow-up visit. General population, general population free of long-standing illness normative score of the ShortForm-36 health survey [53].

substantial improvement in each of the assessed domains: general health ($t_{T0\text{-}T1}$ = -2.92, p = .005, $t_{T0\text{-}T2}$ = -2.65, p = .011), vitality ($t_{T0\text{-}T1}$ = -4.73, p < .001, $t_{T0\text{-}T2}$ = -4.60, p < .001), role emotional ($t_{T0\text{-}T1}$ = -4.52, p < .001, $t_{T0\text{-}T2}$ = -4.95, p < .001), mental health ($t_{T0\text{-}T1}$ = -4.64, p < .001, $t_{T0\text{-}T2}$ = -5.12, p < .001), physical functioning ($t_{T0\text{-}T1}$ = -3.53, p = .001, $t_{T0\text{-}T2}$ = -2.33, p = .025), role physical ($t_{T0\text{-}T1}$ = -4.31, p < .001, $t_{T0\text{-}T2}$ = -3.48, p = .001), bodily pain ($t_{T0\text{-}T1}$ = -3.83, p < .001, $t_{T0\text{-}T2}$ = -2.85, p = .007), and perceived social functioning ($t_{T0\text{-}T1}$ = -4.63, p < .001, $t_{T0\text{-}T2}$ = -4.10, p < .001) (Fig. 3). Moreover, a strong perception of change in health status (change in health: $t_{T0\text{-}T1}$ = -3.58, p = .001, $t_{T0\text{-}T2}$ = -4.78, p < .001) was reported (data not shown). None of the T1-T2 comparisons were statistically significant (Fig. 3).

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4. Discussion

4.1. LAI antipsychotic maintenance treatment from the outside

Since prevention plays a major role in the treatment of any chronic condition, it is important to notice that none of the patients included in the study showed illness relapse or needed hospitalization during the two-year period. This result seems to confirm the importance of a stable AMT in order to minimize the risk of relapse and readmission in schizophrenia independently from the treatment formulation [4–6], while monthly consultations for LAI administration might help outpatients management.

In the present study, we observed a substantial clinical improvement of the sample, with no further treatment-associated side effects or adverse events beside those occurred during the first six months (significant weight gain with olanzapine and symptomatic hyperprolactinemia with paliperidone) in two patients who required a change in antipsychotic treatment and therefore could not complete the study protocol. These results are consistent with previous reports indicating the switch from oral to LAI antipsychotic treatment as a safe and effective intervention to achieve full clinical efficacy in stabilized schizophrenic patients [8,9]. This seems to be further confirmed by the complete patients' adherence to the study protocol.

Changes in patients' psychopathology (in terms of severity of symptoms) were evaluated by expert clinicians who had no therapeutic relationship with any of the participants they assessed, in order to create an objective reference background to address patients' subjective experience of treatment and its relationship with reported functional outcomes. With regard to efficacy on symptoms, we found significant improvements of psychometric indexes one year after the switch to LAI antipsychotic treatment, with no significant changes during the second year, indicating that the overall improvement in psychopathology largely depends on the early phases of LAI-AMT, as previously suggested [35,36]. The significant decrease of mean PANSS total score ($p < .001$) is particularly valuable in clinical practice, since a reduction of at least 25% from baseline is considered as a clinically useful effect [46]. This result is confirmed for all of the PANSS subscales, with a lower level of evidence for the negative symptoms ($p < .01$), which appear less effectively targeted by AMT. Interestingly enough, among clinical features evaluated by the PANSS, those addressed by the general psychopathology subscale seem to be the most influenced by subjective treatment-related factors, such as subjective side effects and attitudes towards drug (i.e. somatic concern, tension, depression, motor retardation, uncooperativeness, disorientation, poor attention, lack of judgment and insight, disturbance of volition, preoccupation, active social avoidance, etc.) [43,46].

An improvement of affective symptoms is evident from the significant reduction in YMRS and MADRS scores, although it was not accompanied by significant changes in the pharmacological treatment of mood symptoms through the study.

The abovementioned results suggest the switch to LAI-AMT as a possible optimization strategy for schizophrenic patients who already achieved clinical stabilization with oral antipsychotics [25,29,30,33,35,36], as well as encourage an early evaluation of LAI SGA use in recently diagnosed patients [8,11,12,42].

4.2. LAI antipsychotic maintenance treatment from the inside

The shift from objectivity to subjectivity has led to well-being, adherence and quality of life becoming key concepts in the treatment of psychotic disorders [18,19]. Their importance is supported by the increasing evidence on the association between positive attitudes towards treatment, subjective well-being and improved functioning and life satisfaction, with a protective value against relapse and readmission risk [5,6,17,20,21]. Perceived well-being under antipsychotics and positive attitudes towards treatment therefore represent central components of recovery from psychotic disorders, as well as a fundamental determinant of patient's compliance and quality of life [17,20]. In the present study, we aimed at evaluating the long-term subjective experience, attitude towards treatment and quality of life of a clinically stable sample of schizophrenic patients after being switched from the oral to the LAI formulation of their AMT.

In this study, we found a significant improvement of all PROs twelve months after the switch that persisted after twenty-four months, suggesting an early stabilization of the perceived benefits in terms of subjective well-being (Fig. 1) and health-related quality of life (Fig. 3).

The lower propensity of LAI antipsychotic formulations to cause adverse subjective experiences of treatment and, in turn, to impair patient's quality of life, could be due to their peculiar pharmacokinetic and pharmacodynamic characteristics [7,8], as well as to other individual and environmental treatment-related factors (i.e. not having to take pills may increase social adaptation, autonomy, and may reduce stigma; periodic treatment monitoring may improve therapeutic alliance, etc.) [5,6]. This is probably due to the fact that LAI-SGAs allow to control titration to effective dose, to steady plasma drug levels (e.g. less peak-to-trough ratio), to avoid first-pass metabolism and to guarantee delivery of medication [7,8]. As said, all of the five SWN-K domains (emotional regulation, self-control, mental functioning, physical functioning, social integration) improved significantly (Fig. 1), and reflected in an enrichment of patients' health-related quality of life in the corresponding areas of daily living (Fig. 3).

A different trend was found for the remarkable improvement in patients' attitude towards drug, with a steady increase of the mean DAI-10 score which proved to be significant in both follow-up periods (Fig. 2). The constant improvement in patients' perception and beliefs about treatment through the study may be related to the experience of persistent clinical benefits and contribute to enhance compliance [9,27,28,35,36].

This seems, at least in part, independent from the level of psychopathology, that remains unchanged during the second year of follow-up. Therefore, the sustained improvement of the mean DAI-10 score throughout the study indicates the possibility of long-term subjective benefits that cannot be explained by a recent change in therapy.

The switch to a LAI-AMT may help to address the subjective core of an optimal recovery, beyond the mere clinical efficacy. Our results, together with the reported superiority of LAI-AMT over oral-AMT in reducing rehospitalization rates [13,14], should lead to consider LAI antipsychotic treatment as a first-line treatment of recently diagnosed psychotic disorders, rather than reserved for the last stages [8,11,12,42].

4.3. Strengths and limitations

Size of the sample and lack of a control group represent major limitations of the present study. Both of these factors are essential to produce solid and generalizable results. However, the findings of this study may be of some clinical interest since, to our knowledge, this is the first mirror study to address a comprehensive group of PROs in a two-year trial on LAI antipsychotic maintenance treatment of schizophrenic patients by presenting real-world clinical experience and focusing on patient's perspective.

The interpretation of our data is limited by factors inherent to open-label studies, and this may imply the risks of bias for internal and external validity [15]. For example, the introduction of a new treatment formulation may bias subjective outcomes due to

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expectancy bias and changes in service provision and utilization. However, the long-term stability of the improvement seen after one year of LAI-AMT seems to exclude that a possible expectancy bias (due to the recent change in therapy) could account for our results. In addition, the design of the wider observational study was tailored to reduce both inter-subject variability and intra-subject variability (patients' clinical and treatment stability, single antipsychotic treatment, fixed antipsychotic drug and regimen).

Due to the mirror design of the present study, we can not exclude that subjects would have reported the same improvements after a similar period of maintenance treatment with the oral antipsychotic they were switched from. Although in a previous six-month case-control study [36], we observed different trends in the change of subjective experience in the LAI and in the oral antipsychotic maintenance groups, long term comparisons including a control group are needed in order to clarify this issue.

The 24-month naturalistic design of the present study implied the variation of the concomitant pharmacological treatment for some patients. These changes were recorded throughout the study. Since the rates of change in concomitant treatments did not vary significantly at any time during the study (Table 1), this variable was not expected to influence our findings on subjective and objective outcomes.

The analytic approach of this study was intentionally not focused on efficacy of different molecules, in the effort of producing an inclusive frame in which to interpret the subjective (rather than the objective), effects of being switched from an oral to a LAI antipsychotic treatment on patient's experience.

4.4. Conclusions

This study indicates possible long-term advantages of switching to a LAI-AMT in terms of subjective experience of schizophrenic patients. In particular, we found a significant improvement of perceived well-being and health-related quality of life after the switch that persisted after 24 months, suggesting an early stabilization of the reported benefits. A noteworthy long-term and constant improvement in patients' attitudes towards LAI-AMT was also found. These results suggest that LAI-AMT may help to address the subjective core of an optimal recovery and should lead to consider this option as a first-line treatment approach in psychotic disorders, possibly as part of a multilevel intervention at the early stage of the illness.

Disclosure of interest

All the authors declare the absence of any potential conflicts of interest, including specific financial interests and relationships and affiliations (other than those affiliations listed on the title page of the manuscript) relevant to the subject of the manuscript.

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References

[1] van Os J., Kapur S. Schizophrenia. Lancet (Lond Engl) 2009;374:635–45.
[2] Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet (Lond Engl) 2016;388:86–97.
[3] Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. Arch Gen Psychiatry 2005;62:975–83.
[4] Emsley R, Chiliza B, Asmal L. The evidence for illness progression after relapse in schizophrenia. Schizophr Res 2013;148:117–21.
[5] Higashi K, Medic G, Littlewood KJ, Diez T, Granstrom O, De Hert M. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. Ther Adv Psychopharmacol 2013;3:200–18.
[6] Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. World Psychiatry 2013;12:216–26.
[7] De Risio A, Lang AP. History and therapeutic rationale of long acting antipsychotics. Curr Clin Pharmacol 2014;9:39–52.
[8] Correll CU, Citrome L, Haddad PM, Lauriello J, Olfson M, Calloway SM, et al. The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. J Clin Psychiatry 2016;77:1–24.
[9] Kaplan G, Casoy J, Zummo J. Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia. Patient Prefer Adherence 2013;7:1171–80.
[10] Lachaine J, Lapierre M-E, Abdalla N, Rouleau A, Stip E. Impact of switching to long-acting injectable antipsychotics on health services use in the treatment of schizophrenia. Can J Psychiatry 2015;60:S40–7.
[11] Stahl SM. Long-acting injectable antipsychotics: shall the last be first? CNS Spectr 2014;19:3–5.
[12] Stevens GL, Dawson G, Zummo J. Clinical benefits and impact of early use of long-acting injectable antipsychotics for schizophrenia. Early Interv Psychiatry 2016;10:365–77.
[13] Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtala J, Hoti F, Jedenius E, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29823 patients with schizophrenia. JAMA Psychiatry 2017;74:686–93.
[14] Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. J Clin Psychiatry 2013;74:957–65.
[15] Haddad PM, Kishimoto T, Correll CU, Kane JM. Ambiguous findings concerning potential advantages of depot antipsychotics: in search of clinical relevance. Curr Opin Psychiatry 2015;28:216–21.
[16] Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. Schizophr Bull 2014;40:192–213.
[17] Marder SR. Subjective experiences on antipsychotic medications: synthesis and conclusions. Acta Psychiatr Scand Suppl 2005;43–6.
[18] Awad AG, Voruganti LNP. The impact of newer atypical antipsychotics on patient-reported outcomes in schizophrenia. CNS Drugs 2013;27:625–36.
[19] Schrank B, Bird V, Tylee A, Coggins T, Rashid T, Slade M. Conceptualising and measuring the well-being of people with psychosis: systematic review and narrative synthesis. Soc Sci Med 2013;92:9–21.
[20] Naber D, Karow A, Lambert M. Subjective well-being under the neuroleptic treatment and its relevance for compliance. Acta Psychiatr Scand Suppl 2005;29–34.
[21] Vothknecht S, Schoevers RA, de Haan L. Subjective well-being in schizophrenia as measured with the subjective well-being under neuroleptic treatment scale: a review. Aust N Z J Psychiatry 2011;45:182–92.
[22] Liberman RP, Kopelowicz A. Recovery from schizophrenia: a concept in search of research. Psychiatr Serv 2005;56:735–42.
[23] Longden E, Read J. Assessing and reporting the adverse effects of antipsychotic medication: a systematic review of clinical studies, and prospective, retrospective, and cross-sectional research. Clin Neuropharmacol 2016;39:29–39.
[24] Chen W-Y, Lin S-K. Comparison of subjective experiences and effectiveness of first-generation long-acting injectable antipsychotics and risperidone long-acting injectables in patients with schizophrenia. J Clin Psychopharmacol 2016;36:492–5.
[25] Niolu C, Bianciardi E, Di Lorenzo G, Marchetta C, Barone Y, Sterbini N, et al. Enhancing adherence, subjective well-being and quality of life in patients with schizophrenia: which role for long-acting risperidone? Ther Adv Psychopharmacol 2015;5:278–88.
[26] Parellada E, Bioque M. Barriers to the use of long-acting injectable antipsychotics in the management of schizophrenia. CNS Drugs 2016;30:689–701.
[27] Kirschner M, Theodoridou A, Fusar-Poli P, Kaiser S, Jager M. Patients' and clinicians' attitude towards long-acting depot antipsychotics in subjects with a first episode of psychosis. Ther Adv Psychopharmacol 2013;3:89–99.
[28] Iyer S, Banks N, Roy M-A, Tibbo P, Williams R, Manchanda R, et al. A qualitative study of experiences with and perceptions regarding long-acting injectable antipsychotics: part I-patient perspectives. Can J Psychiatry 2013;58:14S–22S.
[29] Marinis TDe, Saleem PT, Glue P, Arnoldussen WJ, Teijeiro R, Lex A, et al. Switching to long-acting injectable risperidone is beneficial with regard to clinical outcomes, regardless of previous conventional medication in patients with schizophrenia. Pharmacopsychiatry 2007;40:257–63.
[30] Lloyd K, Latif MA, Simpson S, Shrestha KL. Switching stable patients with schizophrenia from depot and oral antipsychotics to long-acting injectable risperidone: efficacy, quality of life and functional outcome. Hum Psychopharmacol 2010;25:243–52.
[31] Lambert M, De Marinis T, Pfeil J, Naber D, Schreiner A. Establishing remission and good clinical functioning in schizophrenia: predictors of best outcome with long-term risperidone long-acting injectable treatment. Eur Psychiatry 2010;25:220–9.
[32] Macfadden W, DeSouza C, Crivera C, Kozma CM, Dirani RD, Mao L, et al. Assessment of effectiveness measures in patients with schizophrenia initiated on risperidone long-acting therapy: the SOURCE study results. BMC Psychiatry 2011;11:167.

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[33] Rosa F, Schreiner A, Thomas P, Sherif T. Switching patients with stable schizophrenia or schizoaffective disorder from olanzapine to risperidone long-acting injectable. Clin Drug Investig 2012;32:267–79.
[34] Naber D, Hansen K, Forray C, Baker RA, Sapin C, Beillat M, et al. Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia. Schizophr Res 2015;168:498–504.
[35] Pietrini F, Spadafora M, Talamba GA, Godini L, Lelli L, Arcabasso S, et al. The effects of switching from oral to LAI antipsychotic treatment on subjective experience of schizophrenic and schizoaffective patients: preliminary results. Int J Psychiatry Clin Pract 2015;19:106–13.
[36] Pietrini F, Spadafora M, Tatini L, Talamba GA, Andrisano C, Boncompagni G, et al. LAI versus oral: a case-control study on subjective experience of antipsychotic maintenance treatment. Eur Psychiatry 2016;37:35–42.
[37] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM5). 5th ed. Washington, DC: American Psychiatric Press; 2013.
[38] First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute; 2002.
[39] Eli Lilly and Company. ZypAdhera. Summary of product characteristics. EU; 2012.
[40] Janssen-Cilag. Xeplion. Summary of product characteristics. EU; 2012.
[41] Otsuka pharmaceutical. Abilify maintena. Summary of product characteristics. EU; 2013.
[42] Llorca PM, Abbar M, Courtet P, Guillaume S, Lancrenon S, Samalin L. Guidelines for the use and management of long-acting injectable antipsychotics in serious mental illness. BMC Psychiatry 2013;13:340.
[43] Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–76.
[44] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–9.
[45] Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429–35.
[46] Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean? Schizophr Res 2005;79:231–8.
[47] Muller MJ, Himmerich H, Kienzle B, Szegedi A. Differentiating moderate and severe depression using the Montgomery-Asberg depression rating scale (MADRS). J Affect Disord 2003;77:255–60.
[48] Lukasiewicz M, Gerard S, Besnard A, Falissard B, Perrin E, Sapin H, et al. Young mania rating scale: how to interpret the numbers? Determination of a severity threshold and of the minimal clinically significant difference in the EMBLEM cohort. Int J Methods Psychiatr Res 2013;22:46–58.
[49] American Psychiatric Association. Diagnostic and statistical manual of mental disorder. fourth edition Washington DC: American Psychiatric Press; 2000 Text revision.
[50] Nielsen RE, Lindstrom E, Nielsen J, Levander S. DAI-10 is as good as DAI-30 in schizophrenia. Eur Neuropsychopharmacol 2012;22:747–50.
[51] Naber D, Moritz S, Lambert M, Pajonk FG, Holzbach R, Mass R, et al. Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. Schizophr Res 2001;50:79–88.
[52] Ware JE, Snow K, Kosinski M, Gamdek B. SF-36 health survey manual and interpretation guide. Boston, MA: The Health Institute: New England Medical Center; 1997.
[53] Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. BMJ 1993;306 (6890):1437–40.

https://doi.org/10.1016/j.eurpsy.2018.06.002 Published online by Cambridge University Press