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ARTICLE

Self- and caregiver-perceived disability, subjective well-being, quality of life and psychopathology improvement in long-acting antipsychotic treatments: a 2-year follow-up study

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ABSTRACT

Objective: Switching to long-acting injectable (LAI) antipsychotic maintenance treatment (AMT) represents a valuable strategy for schizophrenia. In a recovery-oriented approach, patient-reported outcomes (PROs) such as perceived disability, subjective well-being, and quality of life cannot be neglected.

Methods: Forty clinically stable outpatients with schizophrenia treated with oral second-generation antipsychotics were enrolled at the time of switching to the equivalent dose of LAI. 35 subjects completed this 2-year longitudinal, prospective, open-label, observational study. Patients were assessed at baseline, after 1 year, and after 2 years of LAI-AMT, using psychometric scales (Positive And Negative Syndrome Scale, PANSS; Young Mania Rating Scale, YMRS; Montgomery-Åsberg Depression Rating Scale, MADRS), PROs (Subjective Well-Being under Neuroleptics short form, SWN-K; Short Form-36 health survey, SF-36; 12-item World Health Organisation Disability Assessment Schedule, WHODAS 2.0), and caregiver-reported outcomes (12-item WHODAS 2.0).

Results: No psychotic relapses were observed. Psychopathology measures (PANSS total and subscales – excluding negative symptoms), mood symptoms (YMRS, MADRS), perceived disability (patient- and caregiver-administered WHODAS 2.0), subjective well-being (SWN-K), and quality of life (SF-36) showed a concomitant amelioration after 1 year, without further significant variations.

Discussion: Switching to LAI-AMT may decrease perceived impairment, and increase subjective well-being and quality of life in clinically stable outpatients with schizophrenia.

HIGHLIGHTS

- LAI treatment may improve outcomes by reducing psychopathology levels and relapses.
- In a recovery-oriented approach, patient-reported outcomes cannot be neglected.
- LAI antipsychotics may optimise the subjective experience of treatment.
- Switching to LAI therapy may result in a reduction in perceived disability.
- There is a significant correlation between proxy- and patient-reported disability.

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Schizophrenia; LAI; subjective experience; quality of life; patient-reported outcomes; disability

Introduction

Schizophrenia is a clinically heterogeneous and chronic psychiatric syndrome associated with potentially severe impairment of personal and social functioning (van Os and Kapur 2009; APA 2013). Acute episodes of illness are associated with disease progression and disability (Emsley et al. 2013), which exerts a significant impact on the long-term functional outcome (Wiersma et al. 2000). The definition of disability encompasses a difficulty in functioning at the body, individual, or societal levels, in one or more different life domains, as experienced by an individual with a health condition interacting with contextual factors (WHO 2002; Leonardi et al. 2006). As part of the recovery process (Liberman et al. 2002; Jääskeläinen et al. 2013), reduced disability levels are a goal of schizophrenia treatment. Recovery has been conceptualised as comprising an objective domain, determined by symptom severity and levels of functioning, and a subjective domain, described through various dimensions including quality of life (Vita and Barlati 2018). This model underlines that sustained symptom remission does not guarantee adequate levels of personal and social functioning or subjective well-being. Since functional remission itself cannot neglect subjective experience (Lambert et al. 2006; Schrank et al. 2013), patient-reported outcomes (PROs) need to be evaluated in patient-centered care (Pietrini et al. 2019).

Antipsychotic maintenance treatment (AMT) has an established role in reducing relapses, and long-acting injectable (LAI) antipsychotics seem to minimise this risk (Correll et al. 2016; Tiihonen et al. 2017). Moreover, the use of LAIs in patients with chronic schizophrenia is associated with a reduction in psychiatric services utilisation, as compared to those who are treated with oral antipsychotic drugs (Fang et al. 2020). For these reasons, LAI AMT can represent important therapeutic options to improve the clinical

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course of schizophrenia and its economic burden (Di Lorenzo et al. 2019). An additional emerging property of LAI relates to subjective experience. While AMT itself exerts a significant effect on patients' perception of illness, only the minority of studies directly address therapy-related PROs (Naber 2008; Longden and Read 2016). Second-generation antipsychotics (SGA) have been associated with a better experience of treatment (Awad and Voruganti 2013), and LAI AMT seems to provide better tolerability, possibly through peculiar pharmacokinetic properties (e.g., lack of first-pass metabolism, lower peak-to-trough ratio, and more consistent plasma levels) (Sheehan et al. 2012; Correll et al. 2016). Previous studies showed that switching from oral to LAI leads to better patient-reported outcomes (Witte et al. 2012; Ascher-Svanum et al. 2014), and a project conducted at our clinic highlighted an improved subjective experience of treatment, attitude towards AMT, and health-related quality of life (Pietrini et al. 2015; 2016; 2018). On the other hand, the functional PROs of LAI AMT have not been systematically investigated (Kaplan et al. 2013; Rocca et al. 2016): most studies refer to long-acting risperidone or olanzapine, the psychometric tools are heterogeneous, and most follow-ups are too short to meaningfully address these constructs, as outlined in a recent systematic review and meta-analysis (Olagunju et al. 2019). The complexity of predictors of real-life functioning in patients with schizophrenia stresses the need for integrated and personalised programs (Galderisi et al. 2014; Rossi et al. 2017), and this framework may benefit from patients' and caregivers' perspectives, giving a complementary insight into the individual burden of disease: both a subjective and an objective rating scale are needed to describe the phenomenon of interest (Bowie et al. 2007; Kayes and McPherson 2010). Despite some authors debated over the reliability of the expression of own's health status, possibly related to a lack of insight (Doyle et al. 1999; Bowie et al. 2007), patients' point of view is crucial in functional recovery (Harvey and Bellack 2009).

The primary aim of this study was to conduct an exploratory analysis of self- and caregiver-perceived disability levels after switching from oral to LAI AMT in a 2-year prospective study. The secondary aim was to evaluate the concomitant improvement of psychiatric symptoms in psychometric scales, subjective well-being, and quality of life after switching to LAI AMT.

Methods

Study design

This 2-year, prospective, longitudinal, open-label, non-randomised, single-arm, observational design explored changes in disability and subjective experience of patients diagnosed with schizophrenia, immediately before and during LAI AMT. The data presented are part of the Long-Acting Injectable on Functioning and Experience (LAI-FE) observational project ongoing at the LAI clinic of the Psychiatric Unit of Florence University Hospital (Italy). Three assessments were carried out by an expert psychiatrist (author V. R. or A. B.): a baseline visit (T0, immediately before switching from oral SGA treatment to the corresponding LAI), and two follow-up evaluations after 1 year (T1) and 2 years (T2). Since clinical interventions were not influenced in any way, the study was purely observational. More in details, individual cognitive-behavioral therapy (with a variable frequency and number of sessions) was implemented independently from establishing LAI AMT. All the diagnostic procedures and psychometric tests are part of the routine assessment performed at the clinic. The project protocol was fully explained, and all participants provided written consent to the collection and data analysis. Patient confidentiality was always ensured. The project was 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 was approved by the Independent Ethics Committee of the study centre (reference code: CEAVC 6263_oss).

Participants

Each adult patient with a diagnosis of schizophrenia (APA 2000, 2013) attending our outpatient service between January 2016 and July 2017 who required a long-term antipsychotic treatment was offered to switch to LAI AMT, according to current clinical guidelines suggesting that LAIs should be systematically considered and proposed to any patient for whom AMT is indicated (Llorca et al. 2013).

To confirm the diagnosis of schizophrenia, treating clinicians referred to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (APA 2013) and the Structured Clinical Interview for DSM-IV Axis I Disorders - Patient edition (SCID-I/P) (First et al. 2002), confirming the compatibility between DSM-IV-TR (APA 2000) and DSM-5 (APA 2013) diagnostic criteria.

Inclusion criteria were as follows:

a. age between 18 and 65 years;
b. availability of a caregiver living with the patient (partner, relative, or subject sharing the house with the patient);
c. patient clinically stable on a single oral AMT with either olanzapine, risperidone, paliperidone, or aripiprazole for more than 4 weeks;
d. patient about to be switched to the equivalent maintenance regimen with the LAI formulation of the same antipsychotic, i.e., olanzapine pamoate (Eli Lilly and Company 2012) for olanzapine, paliperidone palmitate (Janssen-Cilag 2012) for paliperidone or risperidone, aripiprazole monohydrate (Otsuka Pharmaceutical 2013) for aripiprazole.

Patients were defined as clinically stable through the following criteria:

- Positive And Negative Syndrome Scale (PANSS) (Kay et al. 1987) total score $\leq$ 120 (not severely ill) (Leucht et al. 2005);
- Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) total score $<$ 30 (not severely ill) (Müller et al. 2003);
- Young Mania Rating Scale (YMRS) (Young et al. 1978) total score $<$ 25 (not severely ill) (Lukasiewicz et al. 2013);
- A score of $\leq$ 4 on each of the following PANSS items: delusions (P1), conceptual disorganisation (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');
- Outpatient status.

Patients were expected to have the possibility to follow the new intervention and to attend regular psychiatric evaluations on the day of the injections. Patients were asked to identify a caregiver living with them to fill the proxy-administered 12-item version of World Health Organisation Disability Assessment Schedule 2.0 (WHODAS 2.0) (Üstün and WHO 2010). The caregiver evaluation was collected at the outpatient facility during a clinical evaluation, in absence of the clinician and the patient.

Exclusion criteria were defined as follows:

- Having been treated with clozapine during the previous 3 months;
- Having previous demonstrated poor response or tolerability to any LAI antipsychotic (i.e., lack of clinical improvement or excessive burden of side effects, according to clinical judgement);

- Current diagnosis of other psychiatric and/or substance use disorders;
- Severe and/or unstable medical condition;
- Neurological and/or cognitive impairment or illiteracy;
- Current or previous symptoms of tardive dyskinesia;
- History of severe drug allergy or hypersensitivity, neuroleptic malignant syndrome;
- For female patients, being pregnant, breastfeeding, or not taking adequate contraception.

54 individuals initiated LAI AMT during the enrolment period; 11 of them did not meet the clinical stability criteria, and 3 did not have an available caregiver or refused to participate. Patients were switched to the corresponding LAI AMT formulation: LAI olanzapine pamoate (300 mg per month for 10 mg/day of oral AMT; 405 mg per month for 15 mg/day of oral AMT), LAI paliperidone palmitate (100 mg per month for 9 mg/day of oral AMT; 150 mg per month for 12 mg/day of oral AMT), and LAI aripiprazole monohydrate (400 mg per month). After the application of the abovementioned inclusion and exclusion criteria, 40 subjects were enrolled. 5 patients did not complete the 2-year study protocol: 2 patients decided to refer to a different outpatient facility of the National Health Service while they were continuing their LAI treatment; 2 patients experienced a depressive, non-psychotic relapse of illness (one after 8 months, another after 9 months, both requiring a substantial change in therapy, including the LAI posology); 1 patient required a change in the AMT due to the onset of relevant treatment-emergent adverse events (weight gain with olanzapine). The final sample consisted of 35 subjects (19 males and 16 females). In accordance with the observational design of the study, patients attending our outpatient facility received a monthly psychiatric evaluation for the whole duration of the study. The outpatient service of our clinic belongs to the National Health System, guaranteeing full accessibility and treatment at no cost for any of the patients suffering from severe mental illness. For this reason, the enrolment did not result in any change in personal expense for the patient.

Assessment

The clinical and psychometric assessment for each patient was carried aside from the routine consultation. Socio-demographic and clinical data were collected at each assessment by expert psychiatrists having no therapeutic relationship with any of the patients taking part in the study.

Three prospective follow-up assessments were made: at enrolment (baseline visit before the switch from oral to LAI AMT at T0), after 1 year of LAI AMT (T1), and after 2 years of LAI AMT (T2). Variations in the psychopathological status of enrolled subjects were evaluated through the changes between follow-up assessments in the mean scores of PANSS, MADRS, and YMRS. The achievement of remission (Andreasen et al. 2005) was evaluated at each assessment as satisfying the following scores:

- PANSS total score $\leq$ 58, and a score of $\leq$ 3 on each of the following PANSS items: delusions (P1), conceptual disorganisation (P2), hallucinatory behaviour (P3), blunted affect (N1), passive/apathetic social withdrawal (N4), lack of spontaneity and flow of conversation (N6), mannerism and posturing (G5), and unusual thought content (G9) (van Os et al. 2006);
- MADRS total score $\leq$ 10 (Hawley et al. 2002);
- YMRS total score $\leq$ 12 (Lukasiewicz et al. 2013).

Outcome measures

At each evaluation, the following PROs were assessed:

a. perceived disability, as measured by the self-administered 12-item form of WHODAS 2.0 (Üstün and WHO 2010);
b. subjective experience of treatment, as measured by the Subjective Well-Being Under Neuroleptics scale short form (SWN-K) (Naber et al. 2001);
c. health-related quality of life, as measured by the Short Form-36 health survey (SF-36) (Ware et al. 1997).

In addition, caregivers reported patients' disability, as measured by the proxy-administered 12-item form of WHODAS 2.0 (Üstün and WHO 2010).

The WHODAS 2.0 is a trans-nosographic scale that evaluates personal and social functioning (Ustün et al. 2010). The DSM-5 (APA 2013) suggests its use as an 'emerging measure' to assess disability (Gold 2014), replacing the Global Assessment of Functioning (GAF) (Endicott et al. 1976) which did not assess disability separately from the severity of mental illness (Gspandl et al. 2018).

The 12-item self-administered version of WHODAS 2.0 (Üstün and WHO 2010) contains 12 questions (S1 to S12) in a Likert-type format with answers ranging from 'None' (0 points) to 'Extreme' (4 points) referring to the difficulties experienced in the past 30 days in various areas of personal functioning (cognition, mobility, self-care, interaction with other people, life activities, and participation in community activities). The overall score is obtained by linear conversion of the raw sum (from 0 to 48), and it ranges from 0 (no disability) to 100 (maximum degree of disability). Since it refers to the previous month, it represents an adequate tool to evaluate clinically stable outpatients. The 12-item form requires 5 min for adequate comprehension and accounts for 81% of the variance in the 36-item version, representing a less demanding assessment when compared to the latter (Ustün et al. 2010).

The 12-item proxy-administered version of WHODAS 2.0 (Üstün and WHO 2010) contains the same items, it provides the same outcome measure described for the patient-administered version, thus representing additional information as a caregiver-reported outcome.

The SWN-K (Naber et al. 2001) is a self-rating scale consisting of 20 items developed to measure the subjective experience of patients receiving AMT. Five subscales consisting of four items each are generated: physical functioning, mental functioning, self-control, emotional regulation, and social integration, with higher scores representing better patient outcomes. The total score ranges from 20 (poor subjective experience) to 120 (optimal subjective experience).

The SF-36 (Ware et al. 1997) is a 36-item self-reported measure of quality of life. The proposed items generate scores for eight domains: general health, bodily pain, physical functioning (patient's ability to perform physical tasks), role physical (ability to perform life role based on physical functioning), role emotional (ability to perform life role based on patient's emotional functioning), vitality, mental health (depression and anxiety), and social functioning (ability to perform social tasks). Each of these scales is linearly transformed into a 0-to-100 scale with higher scores representing better health status. The survey also includes a single item that indicates perceived change in health.

Statistical analysis

Statistical analysis was performed by means of the Statistical Package for Social Sciences (SPSS) for Windows (release 25.0, IBM, 2017). For discrete socio-demographic and clinical variables, absolute and relative frequencies were calculated, and Pearson's chi-square test (χ^2) was performed when appropriate. For continuous

Table 1. Baseline socio-demographic and clinical characteristics of the sample.

N = 35	n (%)
Gender (male)	19 (54.3%)
Marital status (single)	25 (71.4%)
Employed	15 (42.9%)
Age (years)	37.40 ± 11.94
Duration of illness (years)	15.83 ± 10.72
Previous antipsychotics treatments	2.40 ± 1.44
Previous acute episodes of illness	3.26 ± 1.52
Previous hospitalisations	2.17 ± 1.40
LAI antipsychotic treatment	
Olanzapine 300 mg/month	6 (17.1%)
Olanzapine 405 mg/month	17 (48.5%)
Paliperidone 100 mg/month	4 (11.4%)
Paliperidone 150 mg/month	5 (14.2%)
Aripiprazole 400 mg/month	3 (8.6%)

LAI: Long-acting injectable.

variables, descriptive statistics were presented as mean ± standard deviation (M ± SD). Differences between patients' scores at psychometric indexes at baseline, after 12 months, and after 24 months were assessed via repeated-measures ANOVA. Analyses were sex-adjusted. Single comparisons between psychometric indexes at different times were carried out through paired *t*-tests, and Bonferroni correction was used to assess significance. Cohen's *d* was provided to evaluate effect size. To assess the correlation between the caregiver- and the patient-reported outcome on perceived disability (WHODAS 2.0 overall score), Pearson's correlation (*r*) was used for each assessment. The null hypothesis was rejected at an alpha value ≤ 0.05.

Results

Patients and treatment

The socio-demographic and clinical characteristics of the sample are presented in Table 1. No significant changes in the employment status of the patients were registered during the longitudinal assessment. Pharmacological treatments other than AMT were recorded throughout the study: at baseline, 14 patients (40.0%) were in treatment with antidepressants, 18 (51.4%) with mood stabilisers, and no significant changes in polytherapy occurred during the 2 years of follow-up (see Supplementary material).

All patients regularly attended the monthly follow-up psychiatric consultations, which were coordinated with the dates of the injection. No clinically significant treatment-associated adverse events, post-injection syndrome reactions, side effects, or local complications in the site of injections occurred during the study.

Clinical and psychopathological measures

Psychopathology levels evaluated through the presented psychometric indexes are presented in Table 2. After 1 year of LAI AMT, a significant improvement in PANSS total score was registered, as well as in the p-PANSS, and g-PANSS subscales. At the same time, MADRS and YMRS mean scores were significantly reduced after 1 year of LAI AMT when compared to the baseline assessment. All these scales and subscales registered a significant improvement after 2 years of LAI AMT (T0-T2 comparison). Finally, the comparison of the abovementioned measures at T1 and T2 resulted in no significant differences.

Clinical remission was observed in 13 patients (38.2%) at baseline, in 21 patients (60.0%) after 1 year, and in 22 patients (62.9%) after 2 years.

None of the patients required psychiatric rehospitalisation during the 2-year follow-up period, and all but two patients – who were excluded due to relapse with depressive symptoms – remained clinically stable. The patient who dropped out due to weight gain with olanzapine pamoate was switched to another SGA which was available as LAI formulation, but the subject preferred to continue an oral AMT.

Disability scores

Both the proxy-administered and the self-administered 12-item versions of WHODAS 2.0 outlined a significant improvement in the disability overall score after 1 year of LAI AMT, without significant variation after the first year (Table 3). Pearson's correlation between proxy- and patient-reported outcome as WHODAS 2.0 overall score highlighted significant levels of consistency at each follow-up assessment: $r_{T0} = 0.773$ ($p < 0.001$); $r_{T1} = 0.785$ ($p < 0.001$); $r_{T2} = 0.792$ ($p < 0.001$).

Swn-K and SF-36 scores

Patients reported an amelioration of their subjective well-being under LAI AMT when compared to oral AMT (i.e., between T0 and T1, and between T0 and T2; Table 3). First, the SWN-K total score significantly improved after 1 year, and then the change appeared to be sustained. The same pattern was observed for physical functioning, self-control, and social integration. Conversely, emotional regulation and mental functioning improved during the 2-year follow-up but without a significant variation in the first year (Supplementary material). No significant changes were observed between T1 and T2 in SWN-K subscales and total score.

Health-related quality of life, as measured by the SF-36 subscales, showed a significant improvement in all but two areas: physical functioning and emotional role (Table 3). Most subscales showed a significant improvement at T1 and T2 in comparison with T0, without any significant variation in the second year (T1 versus T2): this held true for general health, vitality, mental health, and change in health (Table 3). Bodily pain was reduced after 1 year, but the result was not stable after 2 years; social functioning significantly improved only in the T0-T2 comparison, whereas none of the other comparisons outlined significant differences (Table 3).

Discussion

The aim of the present study was the long-term evaluation of perceived levels of disability, subjective well-being under AMT, and quality of life in a sample of clinically stable patients with schizophrenia switched from an oral to the corresponding LAI antipsychotic.

In a recovery-oriented approach, effective control of psychotic and mood symptoms should be regarded as a basis for any further improvement in patients' subjective well-being, along with the achievement of satisfactory personal functioning and quality of life.

In the present study, the proposed treatment was well tolerated, except for one patient who experienced excessive weight gain with olanzapine, expressing the will of changing AMT. Two patients experienced a depressive relapse which required major treatment adjustment before the T1 assessment, so that it was not possible to conduct a longitudinal follow-up.

Regarding PANSS improvement, the effect on negative symptoms after 2 years of follow-up is in line with the negligible effect

Table 2. Psychopathological characteristics of the sample.

					T0-T1		T0-T2		T1-T2	
N = 35	T0	T1	T2	F(2,66)	t(34)	Cohen's *d*	t(34)	Cohen's *d*	t(34)	Cohen's *d*
PANSS	61.46 ± 23.02	43.46 ± 17.37	44.94 ± 19.24	**13.51*****	**−4.14*****	0.699	**−3.88****	0.656	0.61	0.102
p-PANSS	13.94 ± 5.94	8.71 ± 3.58	8.43 ± 4.00	**21.80*****	**−4.85*****	0.820	**−5.38*****	0.910	−0.50	0.083
n-PANSS	14.09 ± 8.12	11.00 ± 6.94	12.03 ± 8.21	**3.40***	−2.44	0.414	−1.65	0.279	1.07	0.181
g-PANSS	33.54 ± 11.68	23.74 ± 9.49	23.49 ± 9.68	**13.82*****	**−3.79****	0.640	**−4.13****	0.697	−0.22	0.037
MADRS	16.54 ± 8.96	5.89 ± 5.54	7.37 ± 7.62	**37.02*****	**−6.53*****	1.104	**−5.29*****	0.895	1.47	0.248
YMRS	6.46 ± 6.02	0.86 ± 1.66	1.09 ± 2.01	**23.17*****	**−5.30*****	0.896	**−4.86*****	0.822	0.53	0.091

PANSS: Positive and Negative Syndrome Scale total score; p-PANSS: positive subscale of the PANSS; n-PANSS: negative subscale of the PANSS; g-PANSS: general psychopathology subscale of the PANSS; MADRS: Montgomery-Åsberg Depression Rating Scale; YMRS: Young Mania Rating Scale. Bold emphasis highlights significant differences: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

Table 3. Patient- and caregiver-reported outcomes.

					T0-T1		T0-T2		T1-T2	
N = 35	T0	T1	T2	F(2,66)	t(34)	Cohen's *d*	t(34)	Cohen's *d*	t(34)	Cohen's *d*
WHODAS 2.0 overall score										
Patient	31.43 ± 19.06	22.14 ± 21.42	18.33 ± 17.88	**10.57*****	**−2.67***	0.451	**−3.32****	0.561	−1.95	0.329
Caregiver	32.55 ± 19.40	18.91 ± 19.99	17.10 ± 18.95	**18.15*****	**−4.28*****	0.755	**−4.35*****	0.781	−1.29	0.231
SWN-K										
Total score	71.66 ± 22.02	84.11 ± 11.91	85.03 ± 21.17	**8.51****	**2.92***	0.493	**3.08****	0.521	0.44	0.074
SF-36										
General health	50.03 ± 21.14	60.54 ± 23.64	63.80 ± 23.25	**8.92*****	**2.90***	0.490	**2.61****	0.441	1.23	0.208
Bodily pain	71.83 ± 31.84	82.03 ± 26.35	81.74 ± 24.73	**4.79***	**2.54***	0.429	2.01	0.339	0.00	0.000
Physical functioning	75.43 ± 26.13	78.51 ± 27.15	77.00 ± 28.88	0.33	0.71	0.120	0.30	0.049	−0.42	0.070
Role physical	49.29 ± 44.34	63.71 ± 38.09	67.00 ± 40.91	**4.29***	2.19	0.371	2.12	0.358	0.58	0.097
Role emotional	47.63 ± 43.04	63.34 ± 40.02	67.66 ± 41.62	0.49	−0.08	0.013	0.14	0.024	0.62	0.104
Vitality	45.29 ± 19.66	54.69 ± 18.31	56.49 ± 17.48	**8.58*****	**2.66***	0.449	**3.33****	0.563	0.83	0.140
Mental health	52.20 ± 20.91	67.49 ± 18.07	66.17 ± 19.84	**13.33*****	**4.07*****	0.668	**3.48****	0.589	−0.57	0.095
Social functioning	50.72 ± 30.16	62.37 ± 29.14	66.6 ± 25.96	**5.64****	2.03	0.343	**2.55***	0.432	1.26	0.212
Change in health	47.86 ± 29.31	65.51 ± 26.54	72.43 ± 20.56	**11.77*****	**3.07****	0.518	**4.32*****	0.731	1.43	0.242

WHODAS 2.0: World Health Organisation Disability Assessment Schedule 2.0; SWN-K: Subjective Well-Being under Neuroleptics scale short form; SF-36: Short Form-36 health survey. Bold emphasis highlights significant differences: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

of antipsychotics on these dimensions, which refer to various and somewhat non-specific cognitive, functional, and psychopathological areas (van Os and Kapur 2009). On the other hand, the reduction of positive and general symptoms is a target of AMT (Andreasen et al. 2005; Leucht et al. 2005; Lambert et al. 2006). For instance, the general symptoms subscale (g-PANSS) can be influenced by subjective treatment-related factors, with items evaluating somatic concern, tension, motor retardation, and disorientation. The small sample size and the lack of a control group do not allow to draw further conclusions regarding these findings. Conversely, it is important to notice a significant reduction in affective symptoms, in line with the mood-stabilising properties of some SGAs. In general, dimensional symptom severity has a relevant relationship with functional outcomes of schizophrenia (DeRosse et al. 2018), and should not be neglected, especially regarding depressive symptoms (Jin et al. 2001; Dan et al. 2011).

It is important to notice that an increasing number of patients achieved clinical remission (Andreasen et al. 2005) during the follow-up period, mostly during the first year of LAI AMT. Two depressive episodes were managed through major changes in outpatients' therapy and resulted in a dropout from the study protocol. Despite the small sample size, these results seem in line with a large body of evidence on the importance of a regular AMT to improve patients' prognosis (Emsley et al. 2013; Kane et al. 2013). Specifically, patients had already been stabilised on the oral formulation of the same SGA, so these finding might be related to optimisation of therapy through a regular and reliable drug delivery: switching to LAI avoids the risk for partial, covert non-compliance to AMT (Kane et al. 2013). In addition, monthly consultations constitute an occasion of regular outpatient evaluation which may lead to the early detection of psychopathological changes.

For these reasons, switching to LAI-AMT can result in a further clinical improvement of patients who have already been stabilised with oral AMT, indicating a possible optimisation strategy rather than as a second-line option for non-compliant patients (Stahl 2014; Brugnoli et al. 2016; Correll et al. 2016; Stevens et al. 2016; Pietrini et al. 2019).

Subjective well-being in the pharmacological management of psychotic disorders is gaining importance (Naber 2008; Awad and Voruganti 2013; Schrank et al. 2013). In a recovery-oriented approach, a positive attitude towards treatment and a satisfactory quality of life are relevant to compliance, reducing the risk of worse clinical and functional outcomes (Lambert et al. 2006; Kane et al. 2013; Schrank et al. 2013).

Regarding PROs, the present study outlined a significant improvement in most of the scales and subscales presented. The functional evaluation through WHODAS 2.0 is of utmost relevance. In fact, perceived disability deserves attention per se, and it should not be regarded as simply overlapping with severe mental illness (Sartorius 2009). WHODAS 2.0 does not directly refer to psychiatric symptoms (Gold 2014), its use in schizophrenia is increasing (Sjonnesen et al. 2016; Federici et al. 2017; Chen et al. 2020), and it has subsided the earlier WHODAS-II (WHO 2000; Guilera et al. 2012). However, data on LAI antipsychotics as a class are still scarce (Federici et al. 2017).

In this light, the remarkable and stable reduction of perceived disability levels – even if assessed with a simple screening tool –

should be regarded as primarily important: not only the improvement is clear both from patients' and caregivers' point of view, but the correlation between proxy- and patient-administered assessment contributes to the consistency and relevance of the finding. Caregivers' reports should be considered whenever possible: together with patients' reports, they represent the sole significant source of information regarding long-term PROs involving daily functioning and life, and a concordance between the reports in daily clinical practice is likely to give a stronger insight into patients' daily experience. The study sample had strict inclusion criteria, with mild psychopathology levels, regular follow-up attendance, and clinical stability achieved through a single antipsychotic therapy, and it showed a high employment rate when compared to an average of 11.5% to 30.3% (Carmona et al. 2017), so it represents a relatively high-functioning population who may experience more important benefits after switching to LAI AMT, in terms of optimisation of personal functioning. In fact, the found mean disability levels are in line with those seen in wider cohorts of patients with schizophrenia (Sjonnesen et al. 2016), but the follow-up results indicate a remarkable improvement.

Subjective experience of therapy plays a key role in the acceptance of a long-term maintenance treatment (Lambert et al. 2006; Naber 2008), and SWN-K reported a clear improvement after 1 year. Even though the study design does not allow causal inferences, the lower rate of adverse subjective experiences of LAI AMT may be explained by the peculiar pharmacokinetics (Sheehan et al. 2012; Correll et al. 2016), delivering SGAs which are known to present better subjective tolerability (Awad and Voruganti 2013). Moreover, it is possible to hypothesise that subjective experience may be improved secondarily to specific, individual, and environmental consequences of specific LAI AMT properties, such as a better social adaption by avoiding the need for daily oral medication, a subsequent reduction of stigma, and an improvement of therapeutic alliance through monthly psychiatric consultation.

A general expansion in patients' quality of life was observed in some of the subscales which are particularly relevant to psychiatric conditions. More in details, the early and stable improvement in general health, vitality, mental health, and the perceived health change reflected a clear expansion in patients' daily quality of life. Since SF-36 is a trans-nosographic scale that applies to a wide range of medical conditions and to the general population, it investigates non-specific aspects such as physical functioning, physical activity, and bodily pain, all of which showed an unstable and unclear evolution, possibly because of the small size of the sample. In addition, the social integration subscale, which should be regarded as primarily important for adequate interpersonal functioning, presented a significant improvement after 2 years of follow-up.

The link between subjective experience and psychosocial functioning has long been claimed to be crucial (Brekke et al. 1993), but it should be addressed in the light of the new treatments made available for the management of schizophrenia. The present findings are in line with previous studies underlining an improvement of personal and social functioning among subjects who initiate LAI AMT (Ascher-Svanum et al. 2014; Olagunju et al. 2019), although the originality of the design and the choice of different psychometric indexes do not allow direct comparisons. More specific studies allowing causal inference may elucidate the mechanisms underlying the phenomena observed, which include a concomitant improvement of objective outcomes – represented by an amelioration of clinician-administered psychometric scales and by a lack of psychotic relapses of illness – and a wide number of subjective outcomes. These concurrent trends are likely to reflect the known association between symptom severity and quality of life (Watson et al. 2018), but also the fact that an improvement in quality of life is predicted by symptoms reduction and optimal adherence to AMT (Hayhurst et al. 2014). This interplay is likely to be of utmost importance in the early phase of treatment, as seen in a previous study conducted at our clinic which showed a pattern of initial improvement – probably due to adherence optimisation – and a subsequent consolidation of clinical stability (Pietrini et al. 2018).

Some limitations of the present study should be acknowledged. The small size of the presented clinical sample is a major limitation of this study, since solid and generalisable results undoubtfully require a higher number of patients. With this regard, post-hoc statistical power analyses for the sample size ($N = 35$) with three measurements, rejection of the null hypothesis for alpha < 0.05, and small effect size ($f = 0.1$) produced a statistical power of 70%. In addition, the lack of a control group treated with oral AMT does not allow to ascribe our findings to the specific properties of LAI AMT: in other words, we cannot exclude that the same improvement would have been reported after a similar period of oral AMT with the same antipsychotic, even though a previous 6-month case–control study showed clearly different trends between the two formulations (Pietrini et al. 2016). Further limitations are the fact that inter-rater reliability was not evaluated for the present study, and that the lack of specific hypotheses resulted in a high number of analyses. The results still present potential clinical relevance since, to our knowledge, this is the first study to use a wide group of PROs including both a focus on patients' and caregivers' perspectives on disability in a 2-year longitudinal evaluation after switching to LAI AMT in clinically stable patients with schizophrenia.

Open-label mirror studies have raised concerns about the risk of bias for external and internal validity, and research on LAI AMT is no exception (Haddad et al. 2015). However, the long-term stability of most of the results presented regarding the second year of LAI AMT minimises the risk of expectancy bias related to the new formulation and the change in service utilisation. The agreement between patients and caregivers is an important index of consistency of findings. The selection of clinically stable patients, the absence of relevant changes in AMT (fixed antipsychotic drug and regimen), and in concomitant psychotropic treatment minimised the sources of variability. However, the chosen inclusion criteria of clinical stability may have resulted in a study population with milder symptoms and no anti-psychotic polytherapy (which can be regarded as a proxy of the severity of illness), a fact which limits the generalisability of the present findings. For this reason, no data are available for clinically unstable patients – as defined in the Methods – and therefore no assumption should be made for this population.

A possible source of selection bias to be acknowledged is the fact that individuals who dropped out from treatment due to depressive symptoms or side effects – who were therefore lost to follow-up – could have presented worse patient-reported outcomes, resulting in a non-random attrition which may have biased the reporting of the results. On the other hand, larger samples would allow stratification of the population in order to produce more informative data about some clinical subgroups. For instance, the presented sample shows levels of disability at baseline which confirm the findings of wider studies, but the rate of employment in our sample was higher than the average (Sjonnesen et al. 2016). To conclude, patients' quality of life and personal and social functioning are influenced by several factors

that cannot be exhaustively defined by the available socio-demographic and clinical features of the sample, and the present study necessarily represent a simplification in this sense.

Conclusions

The present study outlined possible advantages of switching clinically stable patients with schizophrenia from oral to LAI AMT in terms of subjective experience, mainly assessed through patient-reported outcomes. In fact, a significant and persistent reduction in perceived disability and functional impairment, together with an improvement of subjective well-being under AMT, and an enhanced health-related quality of life, may be of clinical interest for improving functional recovery in patients with chronic and early psychosis.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

The database underlying the present article will be made available on reasonable request to the corresponding author.

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