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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.