

EFFICACY OF LAI IN FIRST EPISODE PSYCHOSIS: AN OBSERVATIONAL STUDY - CLINICAL REPORTS

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SUMMARY

The use of antipsychotics, especially second generation antipsychotics, represents the milestone treatment of "first episode of psychosis" (FEP). Although prodromal symptoms of psychosis have long been recognized, the clinical management of psychotic disorders conventionally begins at the first episode of frank psychosis, as it is well acknowledged that "duration of untreated psychosis" (DUP) is one of the main factor that negatively affects prognosis: a longer DUP is highly correlated to reduced response to treatment, poor clinical and social outcomes, and an overall worst prognosis. Long-acting injectable (LAI) formulations of antipsychotics have traditionally been used for those patients with psychosis with the most severe symptoms, poorest compliance, most hospitalizations and poorest outcomes; moreover it seems that psychiatrists tend to prescribe LAI at the latter stages of the disease. We retrospectively collected clinical and sociodemographic data regarding patients consecutively presenting with symptoms of FEP attending the Community Mental Health Service (CMHS) in Foggia from 1st June 2014 to 31st May 2015. We selected patients who attended the CMHS in Foggia with symptoms of FEP. Different scales were administered to assess symptoms severity, quality of life, side effects, adherence, and overall functionality. In our sample LAI treatment was found to be effective in treating symptoms associated to FEP, improved quality of life and it was associated with a clinically irrelevant incidence of extrapyramidal side effect. Considering that achieving a full symptoms remission in people affected by FEP is associated to better outcomes, and that DUP is associated to poor prognosis, LAIs could play an important role in improving overall recovery.

Key words: first episode psychosis - LAIs - pharmacological treatment - Bipolar Disorder - recovery

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BACKGROUND

Schizophrenia has a chronic course characterized by recurrent episodes of acute psychosis alternating with periods of partial or full remission (75%); it is estimated that only between 14 and 20% of individuals affected by schizophrenia will fully recover (Robinson, 1999; Heres, 2014; NICE guidelines, 2010). For this reason patients require ongoing care for symptomatic control, relapse, prevention and recovery. Increasing evidence shows that antipsychotic discontinuation is associated with relapse in most patients, and the early interventions have a positive impact on long-term outcomes (Heres, 2014; Chien, 2014; Altamura 2012). The use of antipsychotics, especially second generation antipsychotics, represents the milestone treatment of FEP (NICE guidelines, 2010, Canadian Guidelines). SG-LAIs combine the advantages of both the newer antipsychotics (efficacy, fewer extrapyramidal symptoms) and the long-acting formulation; they can reduce relapse through increased medication adherence in patients with schizophrenia (Viala 2012). According to NICE guidelines for schizophrenia, the earlier the treatment started, the less disruptive the effects of the psychotic episode. Moreover schizophrenia is a costly disease characterized by early onset that leads to substantial disability, loss of productivity and frequent use of mental health care resources. Important long-terms

goals of current recovery-oriented treatment plans for schizophrenia in Italy and elsewhere include the enhancement of adherence to medication and rehabilitation through psychosocial intervention involving patients and families (Bartoszki 2011). The combination of antipsychotic medication with other therapeutic interventions is important for the achievement of these long-terms goals. Increasing data suggest that many patients treated in their first-episode of schizophrenia (FEP) respond very well to antipsychotics and can achieve high levels of symptom remission within their first year of treatment, ranging from 70% to 87% (NICE guidelines 2010, Saravan 2010). In fact a strong association between antipsychotic drug treatment discontinuation and relapse (Robinson 1999, APA 2004, Canadian guidelines 2005, NICE guidelines 2010) has been demonstrated. The consequences of relapse faced by patients include the risk of harming themselves or others, impoverishment in personal relationships, discontinuation of education or work and stigmatization, all leading to loss self-esteem and reduced quality of life (Kane 2007). In addition to this, thirty years of neuroimaging studies have produced a wealth of data giving evidence of a potentially progressive nature of disease (Agarwal 2010, Lehman 2004, van Haren 2007). Due to the fact that schizophrenia is a relapsing and evolving condition, it is important to define how long to treat patients in the maintenance phase of schizophrenia: the

5 years following an acute episode are at risk for symptoms relapse, thereafter maintenance therapy should last at least 2 to 5 years (Falkai 2006, Kissling 1991).

It has been suggested (Stahl 2014) that the use of long-acting injection (LAI) formulation of antipsychotics could play a role in treating symptoms related to FEP increasing adherence and promoting a full recovery. However there is still a debate both clinical as ethical about the use of LAI for FEP (Altamura 2012). The aims of the study is to evaluate the use of second-generation long-acting injectable (LAI) antipsychotics in the treatment of FEP in a Community Mental Health Service and then to discuss the potential role of LAIs in improving FEP outcomes.

MATERIALS AND METHODS

We retrospectively collected data regarding patients presenting with symptoms of FEP, both affective and non-affective psychosis (DSM-IV-TR diagnosis), consecutively attending the Community Mental Health Service in Foggia from 1st June 2014 to 31st May 2015 for multidisciplinary treatment that included: individual interviews with psychiatrist and psychologist, psycho-educational activities lead by a trained nurse, cognitive behavioral psychotherapy, or admission to semiresidential rehabilitation facilities.

Clinical and sociodemographic data were collected: psychopharmacological treatment, number and duration of hospitalization, employment or return to school. The following scales were also administered by a trained psychiatrist at baseline and after 3 and 6 months since the enrollment: Brief Psychiatric Rating Scale (BPRS), Health of the Nation Outcome Scales (HoNOS), Global Assessment Functioning (GAF), Extrapyramidal Symptoms Rating Scale (ESRS).

RESULTS

In the observation time, 7 patients presented to the CMHS in Foggia with symptoms of FEP. Those patients were all men, mean age was 33,5 ($\pm 11,5$), the mean DUP ranged from 1 months to ten years. All patients (100%) received a LAI treatment at some point during the course of the illness: the decision to switch from an oral antipsychotic to LAI was due in all cases to lack of compliance, demonstrated by the refusal to take medication and symptoms outburst. Six patients were treated with paliperidone palmitate with doses ranging from 75 to 150 mg and one patient was treated with olanzapine pamoate monthly. The initially prescribed dosage changed over time, according to the evolution of the disease and to the psychiatrist's evaluation: one patient required an increased dosage for relapsing symptoms (hallucinations, delusions, paranoia), in two cases a reduction of LAI dosage was possible. Two patients abandoned the study: one patient went to prison; the other one changed his address and referral care.

In the cohort observed, patients taking LAIs showed an overall improvement in terms of reduced psychotic symptoms, improved quality of life and absence of extrapyramidal side effects. In the observation period, none of them needed to be admitted to the acute psychiatric hospital.

DISCUSSION

Despite the small number of patients observed, the absence of a comparative group and the naturalistic structure of the study, our results not only show that LAI treatment is common in people affected by FEP, but also confirm that LAI could represent a means to achieve symptom remission and reduce the risk of hospitalization in people affected by FEP. Only one patient showed a symptom relapse, but follow-up visits were intensified and an increased dosage of paliperidone palmitate (150 mg) was administered, successfully treating the episode and avoiding admission to the hospital.

Achieving and maintaining clinical remission in people affected by FEP is important, since patients in remission show significantly better social functioning and quality of life: in our cohort, after LAI introduction, all patients could live in their own apartment and return to work. All of them improved their quality of life over time, with more possibility to meet friends and family, to live a more stable and independent life, outside psychiatric hospital. In our cohort treatment with LAIs was also associated with absence of extrapyramidal side effects, symptoms often associated with discontinuation of treatment (Viala 2012), and stigma (Altamura 2012).

In this study LAI treatment was started due to lack of compliance with oral antipsychotic treatment. Compliance is a critical issue across all medical chronic conditions (WHO 2003), including psychosis (Kane 2013): the rate of patients affected by schizophrenia that are partially or completely nonadherent has been estimated to range from 40 to 60% (Olivares, 2009). Partial compliance (defined as compliance to only 50-75% of prescribed antipsychotic for two consecutive weeks or longer) represents a serious problem that may result in abrupt dose changes leading to adverse effects and diminished efficacy, suggesting that it is important to ensure continuous delivery of schizophrenia medication (Bera 2013; Stahl 2014). LAI could reduce relapse through the increased medication adherence in patients with schizophrenia, lower fluctuations in plasma concentrations, lower plasma dose requested.

The majority of patients perceives LAIs as more coercive (Patel 2013; Potkin 2013); however patients are often not fully informed about LAIs by their psychiatrist, and treatment decisions are usually made without patient or caregiver input, with LAIs not being discussed in about 50% of patients taking oral AP (Perkins 2002). Systematic review was carried out to compare effectiveness of typical and atypical LAIs versus oral administration with controversial results,

mostly due to the heterogeneity in methods and interventions used in the reviewed studies (Patel 2013). However FEP usually occurs in younger people aged between 15 and 35 years old, who could potentially prefer to attend the CMHS service only once per months for i.m. LAI instead of taking oral medication every day (NICE guidelines, 2010, Kane 2013; Hyun-Ghang Jeong 2013). It is important to discuss pharmacological issues and therapeutic options with our patients and family members, as it is demonstrated that psychoeducation and patient involvement is associated with better compliance (NICE guidelines, Hyun-Ghang Jeong 2013).

Thirty years of neuroimaging studies have produced a wealth of data (Bartoszki 2011, Altamura 2012) regarding neurodegeneration in people affected by schizophrenia: although the interpretation of these data is often challenging and much remains to be understood, some of the findings suggest that the brain abnormalities observed progress with illness (Agarwal 2010, Bartoszki 2011, van Harren 2008, Kane 2013); by modifying adherence, LAI might potentially impact myelination and account for the better long-term treatment compared to oral treatments (Lehaman 2004). However nowadays the role of LAIs in FEP to prevent cognitive decline induced by demyelination illness related is still a controversial issue (Altamura 2012, Olivares 2009, Bartoszki 2011).

If compared to oral antipsychotics, longer time is required to reach steady-state levels with LAI treatment, the switch from an oral antipsychotic medication to a LAI should be slow (except for Paliperidone Palmitate), moreover side effects associated to LAI are prolonged. Clearly, head-to-head comparison studies between two or more LAIs are critically needed to clarify the role of each compound in the long-term management of psychotic disorders. Further investigation examining the long-term efficacy, safety, tolerability and global outcomes of SG-LAIs compared to oral antipsychotics in FEP or recent-onset schizophrenia are also needed.

CONCLUSIONS

LAI treatment was routinely used in a small sample of FEP attending a CMHS; the use of LAI was associated to symptoms reduction, overall better quality of life and absence of hospitalization. Considering that early intervention in FEP services should be accessible to all people with a first episode or first presentation of psychosis, irrespective of the person's age or the duration of untreated psychosis, using injectable long-acting antipsychotics along with interactive and interdisciplinary follow-up (psychoeducation for patients and caregivers, recovery-oriented programs) could potentially improve the prognosis of FEP and maximize clinical remission. For this reason, LAIs could play an important role in improving recovery with a radical shift in treatment paradigms: from control to care.

More studies with a larger population are needed to investigate long-term side effects of the use of LAI in people with FEP.

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