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Improved insight in first episode schizophrenic outpatients switching from oral to long-acting injectable aripiprazole: a cohort study

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Abstract

The concept of insight into psychiatric disorders is defined as the awareness of illness. Lack of insight is a well-established phenomenon in schizophrenia, with the estimated prevalence of poor insight ranging from 50 to 81%. Konsztowicz S et al. indicated, as the best-fitting model of insight in schizophrenia, five dimensions: 1) awareness of illness and the need for treatment; 2) awareness and attribution of symptoms and consequences; 3) self-certainty; 4) self-reflectiveness for objectivity and fallibility; and 5) self-reflectiveness for errors in reasoning and openness to feedback. Poor insight in schizophrenic patients has been linked to cognitive impairment, increased re-hospitalization rates, worse clinical outcome, psycho-social dysfunction, high risk for suicidality and poor compliance in treatment. Many naturalistic studies proved that long-acting injectable (LAI) antipsychotics improve symptoms, increasing adherence and reducing rates of relapse and hospitalization compared to oral antipsychotic formulations. Twenty-four schizophrenic clinically stabilized first episode schizophrenic outpatients in treatment with oral aripiprazole have been interviewed with the *Positive and Negative Syndrome Scale* (PANSS) at baseline (T0) and six months (T1) after switching to aripiprazole LAI. The difference between the average of total score of PANSS (T1-T0) was statistically significant, evidencing an improvement of general illness (Test t-student $t = -8.108$ ($df = 23$), $p < 0.001$). The improvement of the average score in the sample of three dimensions of PANSS (*Positive Symptoms, Negative Symptoms and General Psychopathology Scale*) (T1) *vs* (T0) was not statistically significant. Considering the item of the PANSS score that measures illness insight (G12), patients were categorized into two groups: good insight (score 1-2, which are in the normal range) and poor insight (score from 3 to 7). The difference of the average score of item G12 between T1 and T0 was statistically significant (Wilcoxon-Mann-Whitney test: -3.17; $p < 0.001$) evidencing an improvement of insight. This result on young patients (average 34.7 years) with normal IQ on insight and the total PANSS scores (T1 *vs* T0) supports the new literature data suggesting the use of LAI at the first-episode psychosis in order to improve the outcomes. Moreover, based on these results, it is hypothesized that the good relationship between efficacy and tolerability (effectiveness) of aripiprazole LAI in long-term treatment leads to a full compliance of the patients. So the authors argued that the improvement of insight would depend on a balanced control of symptoms that allows patients to be clinically stable and at the same time in contact with their own internal world. Finally, the results of this study, suggest that a full and continuous treatment of symptoms could improve insight and consequently functional outcomes and voluntary adherence to pharmacological therapy.

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Introduction

The concept of insight into psychiatric disorders has long referred to the awareness of illness. In 1882, Pick [1] defined the insight as a patient's recognition of "*the pathological aspect of his mental processes, or some part of them, more or less clearly*". Pick hypothesized that insight always involves various *degree of lucidity*, referring to the weakest form as *illness-feeling*, and naming the strongest full-fledged form of insight as *illness-insight*, denoting a cognitive process of conscious reflection and reason.

Insight is a complex construct that entails several dimensions, such as the awareness of specific symptoms and the perceived need of treatment.

According to contemporary models, insight depends on the interaction of neurocognitive [2], social-cognitive and meta-cognitive abilities [3], which form the basis for the development of a coherent autobiographical narrative. Moreover, lack of insight is considered as a shield mechanism against the painful psychotic experience [4]. Konsztowicz S et al. [5] selected, as the best-fitting model of insight in schizophrenia, five dimensions: 1) awareness of illness and the need for treatment; 2) awareness and attribution of symptoms and consequences; 3) self-certainty; 4) self-reflectiveness for objectivity and fallibility; and 5) self-reflectiveness for errors in reasoning and openness to feedback.These components were distinguished between clinical (components 1-2) and cognitive insight (component 3-5). Cognitive insight is considered, nowadays, a malleable target for intervention. Particularly the first aspect is related to awareness of the mental disorder and beliefs regarding the need for medication and hospitalization (*Illness & treatment*). The second one pertains to awareness and attribution of symptoms and consequences of the disorder, as well as attribution or explanation of the illness itself (*Symptoms & consequences*). The third was analogous to the self-certainty subscale of the BCIS (*Beck Cognitive Insight Scale*) [6], or a tendency to be overconfident (*Self-certainty*). The fourth point relates to a willingness to be objective about one's judgments and to acknowledge one's fallibility or likelihood of making errors in judgment. These capacities require self-reflection6 (*Objectivity & fallibility*). The last point involves self-reflection, but relate more to recognizing errors in reasoning and demonstrating an openness to feedback from others. (*Reasoning error & feedback*).

Lack of insight is a well-established phenomenon in schizophrenia, with the estimated prevalence of poor insight ranging from 50 to 81% [7 8]. Poor insight in psychiatric patients has been linked to cognitive impairment, increased re-hospitalization rates, worse clinical outcome, psychosocial dysfunction and poor compliance [9]. The *Clinical Antipsychotic Trials of Intervention Effectiveness* (CATIE) study, a nationwide public health-focused clinical trial of antipsychotic medications, has examined the correlation between insight and poor compliance and they showed how patients with poorer insight, who were most likely to discontinue treatment, also had relatively more severe levels of psychopathology [10].

It has been proposed that the insight also have a bidirectional relationship with social function. Consistent with this, better clinical insight was correlated with better personal and social skills [11] and prosocial behaviour [12] and could predict higher levels of community function, including frequency of social contact and perceived social support [13] and as consequence the capacity to be socially connected [14-17].

On the other hand, poor insight might lead to a worse coping pattern [18], higher level of psychotic symptoms [19], and basic self-disorders [20].

That leads to the conclusion that patients may have different degrees of insight according to the phases of illness [21 22]. Furthermore, many studies demonstrated a strong correlation between poor insight and depression especially linked with psychotic features and feeling of hopelessness, paranoid delusions and ideations [23-25].On the contrary, patients with good insight are at higher risk to be depressed if they have lower socioeconomic status, more severe illness and worse service engagement. Structured, multicomponent psychotherapy might be useful to contrast the onset of depression, and ultimately promote patient's well-being [16].

Many naturalistic studies have demonstrated that long acting injectable antipsychotics improve symptoms while increasing adherence and reducing rates of relapse and hospitalization, compared to oral antipsychotic formulations [26 27]. The efficacy, safety, and tolerability of aripiprazole once-monthly 400 mg (AOM 400) to treat acute exacerbation of psychotic symptoms in adult patients with schizophrenia, has been widely described [28]. Aripiprazole once-monthly 400 mg was superior to placebo based on change from baseline to week 10 in *Positive and Negative Syndrome Scale* (PANSS) [27]. Zahinoor Ismail and al. [29] showed as in patients experiencing acute schizophrenia exacerbation, treatment with AOM 400 and concomitant oral aripiprazole in the first 2 weeks was rapidly efficacious in many aspects of the disease analysed with PANSS. Moreover, treatment with AOM400 had significant results for both short- and long-term outcomes [29]. In our paper we argue that switching from oral aripiprazole to AOM400 in order to treat schizophrenic outpatients could contribute to increase their awareness of the disease and consequently their compliance.

To our knowledge the insight is not an aspect that has been analysed as the core of the compliance and the quality of life of patients in any clinical trial with LAI.

Subjects and methods

Recruitment took place in between 2015 and 2017 among outpatients of the Mental Health Department of Chieti, Italy. Inclusion criteria were a diagnosis of schizophrenia, single episode (FEP) according to the Structured Clinical Interview for DSM-IV (SCID-I-P); age between 18 and 65 and clinical stability, defined as the absence of variation of antipsychotic drug therapy or hospitalization for symptom recrudescence in the 3 months before recruitment. Exclusion criteria were: neurologic disorders; history of alcohol dependence or substance abuse in the past 6 months; moderate or severe mental retardation; recent history of severe adverse drug reactions, such as neuroleptic malignant syndrome; inability to provide informed consent.

Twenty-four schizophrenic clinically stabilized outpatient

(n = 13 male, n = 11 female - mean age: 37.4) in treatment whit oral aripiprazole (10-30 mg/die) were interviewed with the *Positive and Negative Syndrome Scale* (PANSS) at baseline (T0) and six months after the switch to aripiprazole LAI once-monthly 400 mg (T1). The PANSS is a 30- item, 7-point severity scale designed to measure positive and negative symptoms as well as general psychopathology among patients with schizophrenia. The PANSS interview analyse three domains of symptoms: positive symptoms, negative symptoms and general pathology. Each item can berated from 1 (not present) to 7 (extreme). Moreover, the *Scale to Assess Insight* (SAI), the *Scale to Assess Insight - Expanded* (SAI-E Insight) and the *Treatment Attitudes Questionnaire* (ITAQ) were perform.
The interviews were all conducted by experienced and trained clinicians.

Results

Our sample is composed by 24 patients (mean age 34.7) at first episode psychosis. All our patients had a normal IQ and they were clinically stable, in treatment with oral aripiprazole. The difference between the average of total score of PANSS (T1-T0) was statistically significant, evidencing an improvement of general illness [Test t-student t = -8.108 (df = 23), p < .001]. Instead, the difference between the average score in the sample of three dimensions of PANSS (*Positive Symptoms*, *Negative Symptoms and General Psychopathology Scale)* (T1) *vs* (T0) is not statistically significant, according to the fact that the sample was composed by patients with stabilized symptoms (POS_T1 *vs* POS_T0, t = – 0.396 (df = 23), p = 0.695; NEG_T1 *vs* NEG_T0, t = – 0.273 (df = 23), p = 0.787; GPS_T1 *vs* GPS_T0 t = – 0.613 (df = 23), p = 0.546).
Since the main outcome of this study was to analyse the change in insight, we further considered the G12 item of the PANSS at T0 and T1. The difference between the average score G12 (T0) *vs* G12 (T1) is statistically significant highlighting a significant improvement of insight in schizophrenic outpatients when switching from an oral to a long injection formulation aripiprazole in 6 months of LAI therapies (*Test di Wilcoxon Z*: – 3.17; p < 0.001). In the meanwhile, the difference between the average of total score of PANSS (T1) *vs* PANSS (T0) is statistically significant, highlighting a significant improvement of general illness in outpatients who switched from an oral to a long injection formulation aripiprazole after 6 months of LAI therapies [Test t-student (T1 *vs* T0) t = – 8.108 (df = 23), p < 0.001].

Discussion

In this study we tried to select a sample of patients well stabilized, after a first episode of psychosis, with normal IQ. In fact, literature reports that early treatment in firs episode psychosis leads to a better clinical outcome [30,31]. Moreover, a good insight is probably linked to a good cognitive insight and a better cognition of illness [6].
According to this statement, our sample was similar considering age and clinical features. All patients were stabilized with at least 3 months of oral aripiprazole (mean dose 15-20 mg), other treatments were allowed, mainly benzodiazepines for insomnia, but the pharmacological treatment had to be stable for at least 3 months. We did not analysed differences among social and economic status or level of instruction even though that could represent a minimal bias.
Aripiprazole LAI is well known to be well tolerated, with the same efficacy and effectiveness of oral aripiprazole [32], even in patients with resistant schizophrenia [33]. Moreover, compliance was guaranteed because they had to be visited, once per month necessarily, by a specialist.
No one complained important side effects and no one decided to quit the therapy proposed due to collateral effects or intolerance to treatment, witnessing the good tolerability and safety of aripiprazole.
All patients declared an improvement in their quality of life and they felt more aware of their illness.
In literature there is not a trial focused on insight improvement switching from an oral to a long acting antipsychotic, except for one clinical trial by [34]. They analysed many dimensions of pathology in schizoaffective and schizophrenic patients treated with risperidon LAI, finding a good improvement in symptoms and insight as well. So the authors hypothesized that, while the symptoms are well controlled with a stable therapy, the patient could work on his internal world, more aware of his illness but trying to reach a better quality of life. In particular, in our sample, the average of patients at T0 recognized that they had a psychiatric disorder but clearly underestimated its seriousness, the implications for treatment, or the importance of taking measures to avoid relapse. At T1 same sample was just above the upper extreme of normal limits of adequate of their awareness of the disease.
Gaining insight during treatment was associated with higher compliance, reduced risk of suicide and better outcomes, underlining the need to monitor insight over time and tailor interventions according to symptoms and phases of illness [35].
According to the scores of the G12 (*Lack of judgement & insight*) item of PANSS, patients were categorized into two groups: good insight (score 1-2, which are in the normal range) or poor insight (score from 3 to 7). Even though this is only one single item, strong correlations were found with other psychometric tests that investigate the insight such as the *Scale to Assess Insight* (SAI; r = 0.88), *Scale to Assess Insight - Expanded* (SAI-E; r = 0.90), or the Insight and *Treatment Attitudes Questionnaire* (ITAQ).
The improvement in the score of the G12 item was statistically significant, confirming the hypothesis of the authors about the importance of an early intervention and a good compliance.
Limitations of the study were the small sample size, the lack of a control group with oral aripiprazole or with another antipsychotic and probably the short period of observation. Anyway our sample reflects a real world situation since all patients were recruited in a public health care service.

Conclusions

On the basis of the results it is possible argue there is a two-way relationship between a good insight of illness

and a full adherence to treatment with aripiprazole. This may depend on the good relationship between efficacy and tolerability (effectiveness) showed by aripiprazole in long-term treatment [28].

So we argued that the improvement of insight would depend on a balanced control of symptoms that allows patients to be clinically stable and at the same time in contact with their own internal world. We also believe that the improvement of insight must be pursued already at the first episode of illness both with appropriate treatment and with soothing psychotherapeutic and psychoeducational interventions. Finally, the results of this study, suggest that a full and continuous treatment of symptoms could improve insight and consequently functional outcomes and voluntary adherence to pharmacological therapy. Further studies, with bigger sample size and a control group, are needed to confirm these hypothesis.

Conflict of interests

The authors declare that there is no conflict of interests.

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