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Effects of antipsychotic drugs on insight in schizophrenia

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ABSTRACT

Lack of insight is predominant in schizophrenia though the causes are still unclear. The present study was carried on to investigate the effect of three Second Generation Antipsychotics (SGAs) and Haloperidol on insight and the associations among different clusters of symptoms and insight. Fifty-five patients have been recruited at the moment of pharmacological switch needed for psychotic exacerbation, from other antipsychotic drugs to Olanzapine, Aripiprazole, Ziprasidone and Haloperidol. Patients have been followed for 6 months and evaluated at baseline, after 3 months and after 6 months. Regarding the insight improvement, all SGAs resulted more effective than Haloperidol, while no difference was detected among different SGAs. Concerning psychopathology, all SGAs showed a better efficacy than Haloperidol, positive symptoms apart. All SGAs showed a similar efficacy on all domains, except for negative symptoms which resulted less responsive to ziprasidone and haloperidol. An association between improvement of insight and psychopathology was detected. Furthermore, insight appears to be related to psychopathology severity, particularly to negative symptoms. However, the observed different effectiveness of Ziprasidone on negative symptoms and insight suggests that these psychopathological features may be not strictly related and, thus, they may be sustained by different psychopathological processes.

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1. Introduction

According to recent epidemiological data, schizophrenia has a lifetime prevalence of 4.0/1000 individuals worldwide (Saha et al., 2005); moreover, it represents the eighth cause of disability among young people with an important economic burden for the society (Serretti et al., 2009). The disease is characterized by frequent acute relapses, which are due to several causes. Among them, one of the most relevant is the lack of treatment compliance. Poor treatment compliance could be due to several reasons, such as lower tolerability of treatment, complexity of the medication schedule, comorbidity with alcohol consumption, demographical factors (e.g. poor social support), poor relationship with the therapist or presence of delusion of persecution, poisoning or grandeur. However, several studies showed that impaired insight represents one of the main risk factor for lack of treatment compliance (Emsley et al., 2008; Acosta et al., 2012). Consistently, it has been reported that a good insight was one of the main predictor of both a better pharmacological compliance and a better general outcome (Amador and Gorman, 1998). Unfortunately, the lack of insight is predominant among schizophrenic patients compared to other psychiatric patients (Pini et al., 2001), with a prevalence of about 56–67% of poor insight patients (Bayard et al., 2009).

With the term insight we referred to a phenomenological construct, which was described for the first time in 1836 in "Lehrbuch der Psichiatrie", a text by Krafft-Ebingis. In this text the "einsichtslos" (i.e. insight) was considered as the inability of the patient to recognize his delusional aspects (Amador and Gorman, 1998). However, the original definition of insight was enriched later with other aspects. Particularly, nowadays, multi-dimensional accounts of insight have been accepted within research (Konstantakopoulos et al., 2013). David (1990) proposed three distinct but partially overlapping dimensions of insight, namely the ability to recognize that one has a mental illness, compliance with treatment, and the capacity to relabel unusual mental events (e.g. delusions and hallucinations) as pathological. Other authors suggested that two major components of insight are the capacity of patient in recognizing the pathological nature of symptoms (Amador et al., 1993) or the awareness of the benefits of taking the medication (Amador et al., 1993).

Thus, the concept of insight does not include only the awareness of illness, but also the capacity in examining the different levels of motivation and the acceptance of a new point of view that

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could undermine their beliefs (Aguglia et al., 2002). For this reason, the modern scales developed to measure patient's insight are composed by different parts, which investigate all these aspects. Among these scales, the most used nowadays are the Schedule for the Assessment of Insight developed by David et al. (1992) and the Scale to Assess Unawareness of Mental Disorder developed by Amador and Strauss (1990).

In the last years insight has been investigated in relationship with the severity of psychopathology (Hayashi et al., 1999), the acceptance of therapy (Misdrahi et al., 2012) and the cognitive impairment (Markova and Berrios, 1995). Despite some studies investigated these issues, no definitive conclusion has been drawn so far. Particularly, the relationship between insight and psychopathology is still not clear. As a matter of fact, a meta-analysis performed by Mintz et al. showed a weak association among insight and both positive and negative symptoms (Mintz et al., 2003). Unfortunately, few studies investigated the relationship between insight and global psychopathology severity, while a lot of studies investigated the association among insight and different psychopathological clusters, such as positive and negative symptomatological clusters.

Particularly, some authors found that insight was inversely related to positive symptoms, while no association was found concerning the others cluster of symptoms (e.g. negative symptoms) (Kim et al., 1997; McEvoy et al., 1989). Interestingly, the study by McEvoy et al. suggested that the relationship between insight and positive symptoms varied according to the disease phase. Indeed, a relative strong correlation was found during the acute phase of the disease, while this relationship became weaker during the maintenance phase. This observation could be due to the impact of severe psychotic symptoms on the global cognition of the patient, which is related to insight as well. Consistently, from an etiological point of view, it is hard to link positive symptoms directly to insight. Indeed, the more accepted hypothesis posits that lack of insight in schizophrenic patient is due to a prefrontal impairment, which is accountable also for both the negative and cognitive symptoms (Varga et al., 2007). Nonetheless, studies which investigated the association between insight and negative symptoms did not find any correlation (Simon et al., 2009). On the other hand, some studies suggested a possible association between cognitive function impairment and poor insight (Mohamed et al., 1999), suggesting that poor insight may be mainly due to the cognitive impairment of the patient. This finding is consistent with a recent study by Wiffen et al. (2012), which suggests a strong relationship among neuropsychological deficits and poor insight. Interestingly, authors hypothesized a learning component of insight, which may be enhanced through appropriate psychological and rehabilitative treatments.

Nonetheless, overall the relationship between insight and the psychopathological status has not been deeply investigated so far and further studies are required to draw definitive conclusion. Furthermore, to the best of our knowledge, very few studies were specifically carried out to investigate the effects of different antipsychotic drugs on insight.

Despite some limitations in the design and quality of the existing studies on the comparative effectiveness of First Generation Antipsychotics (FGAs) and Second Generation Antipsychotics (SGAs) (e.g. most frequent comparison of SGAs only with haloperidol, heterogeneity in clinical features and population data, etc.), the latter have been proved to be more effective in improving negative symptoms (Hartling et al., 2012). On the other hand, the superiority of SGAs on FGAs on cognitive symptoms is still controversial (McKenna and Mortimer, 2014). Taking into account these data, it could be hypothesized that SGAs may have a specific effect on insight as well. Consistently, one preliminary study by Aguglia et al. showed that SGAs improved patients' insight more than FGAs (Aguglia et al., 2002). Nonetheless, the sample size of this previous study was small and it did not allow to draw consistent conclusions as well as to compare the effects of different SGAs. However, the detection of a specific effect on this fundamental psychopathological aspect by a specific antipsychotic drug may allow to better understand the biological origin of insight and its relationship with other symptoms, also in providing important clinical information.

Taking into account all these considerations, the present study was carried out to investigate the specific effect of three SGAs (aripiprazole, olanzapine, ziprasidone) and one FGA (haloperidol) on insight in a sample of schizophrenic patients, which needed a pharmacological switch for psychosis exacerbation. As secondary aims, we investigated the associations among different clusters of symptoms and insight, also considered in its distinct components, in order to provide further evidences for previous literature data.

2. Methods

We included in the study 55 patients recruited at the Department of Psychiatry of University Hospital of Catania, Sicily, Italy. The diagnosis was made by two different M.D. according to the DSM-IV TR criteria. The duration of study was 6 months and there were three times of follow up: at baseline (T0), at 3 months (T1) and at 6 months (T2). All recruited patients needed a pharmacological switch for psychosis exacerbation at the inclusion in the study. All patients (18–65 years old) provided written informed consent before participating in the study. The study was carried out in accordance with the latest version of the Declaration of Helsinki. At the recruitment, patients were assigned randomly to one of the antipsychotic included in the present study. The drugs used were chosen because (1) haloperidol (HAL) is the most used FGA in our country and worldwide; (2) olanzapine (OLA) is one of the SGA with more proven efficacy (Glick et al., 2011); (3) aripiprazole (ARI) is one of the SGA that seems to have a greater effectiveness on both negative and cognitive symptoms in comparison to other SGAs (Stip and Tourjman, 2010) and (4) ziprasidone (ZIP) is one of the newest SGAs in our country and its effect on specific psychopathological features has not been deeply investigated so far (Montes, 2012). Fifteen patients were switched to OLA, 15 to HAL, 15 to ARI and 10 to ZIP. The switch was made gradually. The range of dosage of antipsychotics was 10–20 mg for OLA, 2–9 mg for HAL, 10–30 mg for ARI and 80–160 mg for ZIP. The psychopathological status of patients was measured at each visit through the administration of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989), by a trained rater, who was blinded to the patients' treatment. Levels of insight were assessed by the same rater through the administration of the Schedule for the Assessment of Insight (SAI) (David et al., 1992), a semi-structured interview that measures three different dimensions of insight: therapy compliance (SAI 1), awareness of illness (SAI 2) and identification of psychotic symptoms (SAI 3).

The improvement at PANSS scale was calculated with the formula [(PANSS T0-30)−(PANSS T2-30)/(PANSS T0-30)] and the improvement at SAI scale with the formula [(SAI T0)−(SAIT2)/(SAIT0)]. The improvement of each PANSS and SAI subscales (respectively positive, negative and general subscales and SAI1, SAI2 and SAI3) was calculated and considered for the analyses. All data analyses were performed using the Statistica package, version 7.0 (StatSoft Italia, Vigonza, Padua, Italy) for Windows® (1995). Analysis of variance (ANOVA), analysis of co-variance (ANCOVA) and chi-square statistical analyses were performed when appropriate. All p-values were 2-tailed. GPower (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower/) was employed for the power analysis. With these parameters ($p=0.05$) we had a sufficient power (0.80) to detect an effect size of 0.2, that corresponded to the possibility of detecting differences on PANSS total improvement scores of two points.

3. Results

The characteristics of the sample are shown in Table 1. The groups of patients, separated by the antipsychotic drugs, were homogeneous for age, sex, PANSS and SAI scores at the baseline (Table 1).

Regarding insight, analyses showed that patients of the HAL group showed a lower improvement compared to SGAs patients (overall $p<0.001$, HAL vs OLA $p<0.001$, HAL vs ARI $p<0.001$, HAL vs ZIP $p<0.001$) (Fig. 1). Among the SGAs, no difference was detected in improving insight. When we controlled for possible confounding factors, we found that a higher psychopathology at the baseline predicts a higher improvement in insight (PANSS

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