TITLE

Treatment response of neurological soft signs in drug-naïve patients with a first psychotic episode

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CONFLICT OF INTEREST

All authors report no conflict of interest.

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ABSTRACT

Background: Neurological soft signs (NSS) are intrinsic features of psychosis that appear years before beginning a drug treatment. However, whether NSS respond to antipsychotics and whether these changes are clinically reliable and significant remains to be seen.

Objective: We sought to determine the effect of antipsychotics on NSS in a first-episode psychosis (FEP) sample who had never exposed to antipsychotics.

Methods: We included 100 antipsychotic-naïve patients with FEP in this study. 77 patients completed the study assessments at baseline, 1 month and 6 months. The Neurological Evaluation Scale (NES) evaluated NSS. Patients were alternatively selected to receive risperidone or olanzapine treatments and continued participation in their mental health setting during follow-up with one of four treatment groups: risperidone, olanzapine, mixed antipsychotics or no medication. We also included a control group of 28 healthy volunteers.

Results: Treatment groups showed a statistically significant improvement on total NES scores and most NES subscales except for 'frontal signs', regardless of antipsychotic allocation. NSS changes were reliable; however, there was great variation in the total NES scores between treatment groups, ranging from 4% to 24%. Clinically meaningful changes (CMCs) on total NES scores ranged from 25% to 50%. Six patients (7.8%) demonstrated a reliable and CMC on total NES scores.

Conclusions: NSS improved significantly over follow up regardless of the treatment regimen assigned to antipsychotic-naïve patients with a FEP. However, only 6 (7.8%) achieved a reliable and clinically meaningful improvement. The pattern of response of NSS to antipsychotic drugs evidenced both state and trait characteristics.

KEY WORDS: neurological soft signs, psychosis, schizophrenia, first-episode psychosis, drug-naïve patients, never-treated patients.

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INTRODUCTION

Neurological soft signs (NSS) include a wide range of sensory and motor performance abnormalities that do not implicate a specific brain region or neurological syndrome (Heinrichs and Buchanan, 1988). NSS exist along a continuum of psychiatric and neurologic illnesses, but they are more prevalent in schizophrenia (Bombin et al., 2005; Buchanan and Heinrichs, 1989; Dazzan et al., 2008; Dazzan and Murray, 2002; Picchioni and Dazzan, 2009). Although they lack specificity (Bombin et al., 2005), NSS may indicate a vulnerability to develop a brain disorder (Fish, 1987) because they are often found years before the onset of schizophrenia. And NSS have been proposed as schizophrenia endophenotypes (Chan and Gottesman, 2008) because they are familial in nature and segregate with illness (Chan et al., 2010).

Although antipsychotics could be another cause of NSS (Gupta et al., 1995; Madsen et al., 1999), the presence of NSS in antipsychotic-naïve patients with a first-episode psychosis (FEP) demonstrates that NSS cannot be explained by antipsychotic exposure alone (Browne et al., 2000; Buchanan and Heinrichs, 1989) or their side effects (Boks et al., 2003; Browne et al., 2000; Lawrie et al., 2001); however, there is still a lack of agreement on this point (Gupta et al., 1995; Prikryl et al., 2006; Scheffer, 2004).

Moreover, there are controversies regarding to what extent NSS are trait or state markers of schizophrenia or psychosis. Some studies have reported temporal stability (Chen et al., 2005; Madsen et al., 1999) or even a progression in a subset of patients (Madsen et al., 1999). Other authors suggest that NSS are state markers for schizophrenia (Bachmann et al., 2005; Scheffer, 2004; Whitty et al., 2003). NSS can also adopt mixed features while remaining moderately stable, although oscillations depend on state variables (Bachmann et al., 2005; Bombin et al., 2005; Prikryl et al., 2007).

Many studies have addressed the temporal stability of the course of NSS in schizophrenia spectrum disorders, but none have specifically addressed the comparative effectiveness of antipsychotics on NSS. In addition, as psychiatric treatment outcomes are often equivocal in practice and research, the distribution of normal and abnormal responses often overlap and statistical differences between groups do not convey reliable or clinically meaningful results. Thus, the use of multiple analytical approaches based on objective assessments might disentangle statistically significant differences from those that are reliable and clinically meaningful (Evans et al., 1998; Jaeschke et al., 1989).

Traditionally, NSS changes have been considered as correlates of psychopathological symptoms and changes in NSS have been attributed to improvement of symptoms related to treatment response (Bombin et al., 2005). However, NSS changes can be accomplished by both state-dependent and trait-like components, which respectively may fluctuate with clinical course or even worsen with illness progression (Whitty et al., 2003).

This study aimed to examine the response of NSS, as main outcome measure, to different treatments in a sample of antipsychotic-naïve patients with FEP followed-up in their naturalistic setting. Our goal was not only to examine whether NSS changes after a 6-month

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follow up were statistically significant, but also whether they were clinically reliable and significant.

We hypothesized: 1) that NSS would improve over time. 2) this improvement would differ among the final allocation treatment groups at the follow up. 3) that patients will continue to have significant differences on the NSS relative to healthy control.

METHODS

Patient population

Patients' sample and assessment procedures have been described in detail in previous reports (Cuesta et al., 2009). 100 previously antipsychotic-naïve patients with FEP comprised this study. We followed up with these patients 6 months later.

To be included in this study, patients must: (1) be aged 16–65 years, (2) have had an acute psychotic episode that met DSM–IV–TR criteria (APA, 2002) for schizophrenia and schizophrenia spectrum disorders at intake, (3) have not been exposed to antipsychotics, and (4) have provided written informed consent and been able to participate in a neuropsychological assessment. We excluded patients with primary affective disorders and patients with a history of serious medical or neurological disease, head injuries or mental retardation. Patients with lifetime drug abuse or drug dependence (DSM IV-TR criteria) were not included.

In addition, we included 28 healthy control volunteers (19 men and 9 women). To be included in this study, control participants must: (1) lack major psychiatric disorders, including drug or alcohol abuse, (2) not have a first-degree relative with a major psychiatric illness, and (3) not have been on a psychopharmacological treatment.

Study design and procedures

We conducted a comprehensive psychopathological and neurological assessment at three time points: baseline (24-48 h before starting treatment) as well as 1 and 6 months after baseline. All patients underwent the Comprehensive Assessment of Symptoms and History interview (Andreasen et al., 1992) for the psychopathological assessment. Once we completed the baseline assessment, patients were assigned alternated between the two treatments (risperidone or olanzapine drugs). After discharge, patients' psychiatrists treated them at home under the recommendation that they continue their monotherapy regimen. If indicated by their psychiatrist, patients received either biperidene or benzodiazepines.

The final drug allocation groups consisted of: patients taking risperidone (n=29); patients taking olanzapine (n=22); patients whose medications were mixed (e.g., if their psychiatrists switched or combined the initial prescription; n=16); and patients who did not receive antipsychotics during the last 3 months of the follow up (n=10).

During follow up, 23 of the 100 initial patients withdrew from the study; hereafter, the dataset consisted of 77 patients (53 men and 24 women).

Doses of the atypical antipsychotics were transformed to chlorpromazine equivalents (mg) (Woods, 2003). Patients received either biperidene or benzodiazepines if needed by indication of the treating psychiatrists.

Neurologic examinations

The Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989) evaluated NSS. This 26-item scale results in a total score and four subscale scores: sensory integration, motor coordination, sequencing of complex motor acts and others. Because the others subscale is heterogeneous, we removed the frontal signs and used the split-half method. We divided the new frontal subscale into two halves and examined the coefficient alpha between them. Consistency was reached because both halves showed excellent internal consistency (Spearman-Brown coefficient=0.934 vs. 0.923). The two evaluators (MSC and EGJ) were blind to the treatment assignment and they achieved high inter-rater reliability coefficients for neurological assessments: Cronbach's alphas for the NES sensory integration, motor coordination, sequencing of complex motor acts, frontal signs, and others subscales as well as the total score were α=0.981, α=0.721, α=0.966, α=0.883, α=0.939, and α=0.986, respectively.

Statistical analyses

A set of Kolmogorov-Smirnov tests found that all NES scores were normally distributed.

To account for the effects of treatment and time, we performed a repeated-measures ANOVA with NES scores (at baseline, 1 month, and 6 months) as the within-subjects dependent variable and treatment assignment (risperidone, olanzapine, mixed or no antipsychotics) as the between-subjects factor. A Bonferroni correction adjusted the alpha level for multiple comparisons (p=0.008). When appropriate, we applied the Greenhouse-Geisser correction for sphericity violations.

To better characterize changes in NES we estimated whether these changes have or not clinically significance. The clinical significance of a treatment is usually based upon external standards provided by clinicians, patients and/or researchers (Kraemer et al, 1994). In Psychiatry, the assessment of functioning provides the typical outcome measure for clinical significance in many studies and in practice. Even though NSS are measurable through standardized scales, their intensity does no usually convey clear or direct effects on functioning measures. NSS not only are subtle neurological manifestations but also many of them should be elicited to be ascertained. Thus, we estimated the Reliable Change Index (RCI) (Cuesta et al., 2009; Jacobson and Truax, 1991) in all four treatment groups.

The RCI evaluates whether patient change is unlikely to be caused by a single measure of unreliability. Usually, RCI requires that a matched, healthy control group is reassessed using the same instruments and within the same timeframe as the experimental groups; however, because we only evaluated our control group at baseline, Cronbach's alpha coefficient assessed the NES total and subscale scores between baseline and the 6-month follow up as suggested by classic reliability theory (Evans et al., 1998). The coefficients for total score,

sensory integration, motor coordination, sequencing of complex motor acts, frontal signs and others were α=0.59, α=0.43, α=0.38, α=0.48, α=0.12 and α=0.6, respectively.

Contingency tables were arranged to integrate reliable and clinical significance changes for NES total score and subscales in total sample and by treatment groups.

In addition, we calculated whether the change after the treatment was clinically meaningful by determining the cutoff point according to Evans et al.'s C criterion (Evans et al., 1998). Because of the control group, we were able to test whether patients moved from a clinical distribution to a normative distribution after treatment. The cutoff point was the probability that coming from either distribution was equal.

$$(mean_{clin} \times SD_{norm}) + (mean_{norm} \times SD_{clin})/SD_{norm} + SD_{clin}$$

The results were: total score (8.07), sensory integration (2.46), motor coordination (0.66), sequencing of complex motor acts (1.89), frontal signs (0.11) and others (3.47).

Finally, in order to explore whether changes in NSS scores parallels the psychopathology ones Pearson correlation coefficient analysis was used. And specifically the relationship among clinical change on positive, negative, and disorganization scores and NSS change scores was examined. The clinical syndromes significantly associated with NSS change scores were used as covariates in repeated-measures ANOVA analysis.

We conducted analyses using SPSS 17.0.

RESULTS

Background characteristics

There were no clinical or socio-demographic differences at baseline between patients who withdrew (n=23) and those who did not (n=77), except the former group had more years of education (t=2.36, df=98, p=0.020). There were no differences in NES scores between groups (F=1.114; p=0.294).

Patients and controls had significantly different marital statuses; a higher proportion of patients were single. NES scores were significantly higher in patients compared to controls (Table 1).

We did not find significant differences between the four treatment groups in clinical or socio-demographic characteristics. Patients showed a significant improvement over time in the psychopathological symptoms (Table 1).

The average doses of antipsychotic drugs by treatment group at the second evaluation in chlorpromazine equivalents (mg) were: risperidone 318.96 (133.90), olanzapine 227.27 (108.81), mixed 296.87 (176.27), and no antipsychotic drug group 232.5 (137.96). These doses at third evaluation were risperidone 214.65 (145.54), olanzapine 156.81 (102.69), mixed 295.83 (318.14), and no antipsychotic drug group 0.00 (0.00). The mean daily antipsychotic doses for the whole treatment period (obtained following the method of Ho et al., 2011) were: risperidone

228.02 (134.72), olanzapine 157.19 (69.49), mixed 279.34 (259.58), and no antipsychotic drug group 37.91 (22.34). Finally, the mean daily doses for the first month and for the rest of evaluation period were included in our previous paper (Cuesta et al., 2009). No differences in chlorpromazine equivalents (mg) between the four treatment groups were initially found, though risperidone group received higher antipsychotic doses at 6-month and they were treated more often with anticholinergic drugs (37.93%) than either the mixed (18.75%) or olanzapine and no-antipsychotic groups (0%), as it was reported elsewhere (Cuesta et al., 2009).

There not were significant differences in mean SAPS and SANS total scores among the four groups ($F= 2,104$, d.f. 3, $p\leq0.107$; and $F= 0.456$, d.f. 3, $p\leq0.714$, respectively)

Treatment effects

The NES total score and all subscale scores, except frontal signs, significantly improved over time after a Bonferroni correction (Supplementary Table 1). However, we did not find significant differences related to treatment group. Moreover, the only significant interaction we found was between group and time in the sensory integration subscale. Taking into account that positive and disorganized syndrome change scores positively correlated with NSS change scores, they were used as covariates in repeated-measures ANOVA analysis. The inclusion of these covariates made statistical significances for time effect disappear, but did not alter the results of differences in group, and group by time interaction reported (Supplementary Table 1). Subsequent pair-wise comparisons between treatment groups did not yield significant differences. There were similar results when we examined the subset of patients with NSS total score below the mean at baseline (NES total score $\leq$ 17).

Sixty-five patients (84.4%) showed a reliable stable pattern in NES total score during the follow-up and for 12 patients (15.6%) the pattern was of improvement in total NES scores over time. After examining NES subscales scores in the total sample, we identified 5 patients who showed worsening in sensory integration (n=1, 1.3%), motor coordination (n=1, 1.3%) and frontal signs (n=3, 3.9%) (Table 2).

However, it is worth noting that although the predominantly pattern of NES total score was stable in the four treatment groups, there was a great variation between the percentages of improvers and stable patients among the four treatment groups: 24.1% versus 75.9% in the risperidone group, 4.5% versus 95.5% in the olanzapine group, 18.8% versus 81.3% in the mixed treatment group, and 10% versus 90% in the no antipsychotic group, respectively (see Supplementary Table 2).

We defined clinical meaningful change as a practical or applied value of treatment effect. Supplementary Table 3 shows the percentages of patients with clinically meaningful estimates. 13 patients (16.9%) started below the clinically meaningful change (CMC) criterion for NES total score, and 40 patients (16.9%) started above the CMC criterion for NES total score, but did not achieve CMC over time. Moreover, we found a great amount of variation among treatment groups in NES total score CMC. Whereas 50% of the non-medicated patients

and 40% of the patients treated with olanzapine showed a CMC, only 25% of patients in mixed group and 20.7% of the patients on risperidone showed the same effect.

To account for reliability and CMC, we cross-tabulated both measures for NES total and subscales scores. As Table 2 shows, the percentage of patients who showed both reliability and CMC was below 10% for the NES subscales and 7.8% (N=6) for the total NES score. Moreover, for some subscales, such as frontal signs and others, reliability and CMC were minimal (1.3% and 3.9%, respectively).

Figure 1 visually displays the results before and after treatment. The grey area of the figure denotes patients who demonstrated both reliability and CMC on the NES total score. Three of these patients were in the risperidone group, 2 were in the mixed treatment group and 1 was in the non-antipsychotic group (Table 3). We found similar results for the rest of the subscales (Supplementary Table 3).

DISCUSSION

Main findings

This study examined response to NSS treatment over 6 months in a drug-naïve sample with FEP. Patients were alternatively assigned to risperidone or olanzapine treatment groups and followed up in a naturalistic setting. To our knowledge, this is the first longitudinal study that statistically compares NSS scores among different treatment groups and assesses whether these changes are reliable and clinically meaningful.

Our results support six points: first, NSS were prevalent in drug-naïve patients with FEP; moreover, both NES total and subscales scores were significantly higher in patients versus healthy controls; second, patient NSS improved significantly over time; third, this improvement occurred regardless of treatment assignment or any modification made to the drug regimen by their treating psychiatrist but it was partly related to improvement in positive and disorganized syndromes; fourth, the improvement in NSS was reliable for less than one quarter of the sample (n=12, 15.6%); fifth, our results were clinically meaningful in approximately one third of patients (n=24, 31.2%); and sixth, only a minority of patients reliably moved toward the normal range of NES scores (n=6, 7.8%).

The prevalence of NSS shown at baseline agrees with studies reporting that between 88% and 100% of patients with schizophrenia present at least one NSS (Whitty et al., 2006). Other studies have reported a smaller prevalence ranging from 50% to 65% (Bombin et al., 2005; Heinrichs and Buchanan, 1988).

Based on the association between NSS and more severe forms of psychosis, the prevalence of NSS might be lower in patients with FEP compared to chronic samples. However, in a recent study of FEP patients, the percentage of patients who scored abnormally on the NSS examination was 78%. This study did not test antipsychotic-naïve patients exclusively (Dazzan et al., 2004). A systematic review of the prevalence of NSS found that they varied from 20% to 97.1% in patients with FEP (Dazzan and Murray, 2002). Furthermore, a recent review of 11 studies concluded that 20% of antipsychotic-naïve patients experienced increased rates of

NSS before beginning their treatment. Similar rates had been previously reported in a review of empirical studies (Wolff and O'Driscoll, 1999).

The literature has shown a high variability in both the prevalence and the course of NSS in patients with schizophrenia. Studies that have focused on the long-term temporal stability of NSS report that NSS increase over a 3-year period; progress in chronic patients (Madsen et al., 1999); improve in both chronically institutionalized patients with schizophrenia or FEP over a 5-year period (Prikryl et al., 2007; Whitty et al., 2003); and remain stable from 12 months (Emsley et al., 2005) to 3 years (Chen et al., 2005).

Regarding the effect of antipsychotics on NSS, short-term outcomes of NSS remain controversial because other studies demonstrate that antipsychotic treatments in naïve patients do not relieve (Gupta et al., 1995; Scheffer, 2004) or worsen, some NSS symptoms (Merriam et al., 1990). In a summary of these results, some authors conclude that current or lifetime antipsychotic doses do not influence the severity of NSS (Bombin et al., 2005). Boks et al. reported that NSS increase after beginning an antipsychotic treatment, which suggests there are potential iatrogenic effects on NSS (Boks et al., 2003). However, Goldstein et al. found that neurological dysfunction was reduced in the on-drug relative to the off-drug condition (Goldstein et al., 2005). In addition, NSS seem to be independent of the type of antipsychotic used because studies found no differences between typical and atypical antipsychotic treatments (Bersani et al., 2005). However, the effect of specific antipsychotics on NSS has not been established because previous studies have addressed this issue indirectly by assuming that NSS are a corollary of psychopathological symptoms or clinical status (Tosato and Dazzan, 2005).

Our patients' NES total and subscale scores, except frontal signs, significantly improved over time. Dissociation in response to treatment of NES subscales may add evidence to a differential pathogenesis of NES subscales in psychosis (Dazzan et al., 2008; Whitty et al., 2003). While NES subscales improving with clinical symptoms and antipsychotic treatment (sensory integration, motor coordination, sequencing of complex motor acts and others subscales) might represent 'state' marker of neurobiological dysfunction that fluctuates with the improvement of symptoms, frontal signs seem to be enduring characteristics of psychosis present at its earlier stages that might be related to brain structural abnormalities in basal ganglia and cerebellum (Dazzan et al., 2008). Moreover, this treatment-related improvement of certain NSS is in agreement with the studies that have demonstrated that antipsychotic treatments ameliorate NSS (Bachmann et al., 2005; Goldstein et al., 2005; Whitty et al., 2003) and with studies that have attributed this change to an improvement in clinical status (Bachmann et al., 2005; Scheffer, 2004; Whitty et al., 2003), particularly negative and disorganized symptoms (Bombin et al., 2005; Tosato and Dazzan, 2005).

NSS improvement occurred regardless of treatment assignment, although atypical antipsychotics were the only type of drug prescribed in this study. Moreover, the improvement of patients who did not receive treatment since month 3 of the follow up suggests that the

beneficial effect of antipsychotics occurred during the first weeks of treatment and lasts for at least 6 months.

NES examinations involve the interplay between patient and observer's ratings. Like many standardized tests, the NES is not exempt from biases such as the effects of intervening variables, practice, chance and measurement errors. The NES has acceptable test-retest reliability (Buchanan and Heinrichs, 1989; Sanders and Keshavan, 1998); however, the extent to which patients improved beyond the range of the instrument's measurement variability has not been previously ascertained. In this regard, because there is no well-established standard for determining clinical significance in NSS and because it was not possible to derive it from normative data, we chose a statistical approach to determine the amount of variation in NSS exceeding chance for this study.

The RCI accounts for this measurement variability, chance (Evans et al., 1998) and practice effects (Heaton et al., 2001).

In addition, to assess whether a patient's improvement is clinically meaningful, clinicians need to know to what extent their score exceeds the range of a normal group. A minority of our patients showed a reliable and CMC in NSS over time, which allowed us to detect these individuals. No patients showed a reliable or clinically meaningful deterioration of NSS.

Our approach overcomes analytical strategies focused on significant differences between groups, since identifying reliable and CMCs at group and individual levels might allow researchers to characterize the improvement or deterioration of patients, which is usually obscured in group tendencies.

There is a close relationship between improvements in response to drug treatments and the conceptualization of NSS as a trait (Bombin et al., 2005; Chan et al., 2009). However, the trait versus state debate is not mutually exclusive because our results leave room for both features (Kraemer et al., 1994). Our patients improved over the 6-month follow up, which suggests that NSS are at least partially state-dependent; however, they remained above the normal range displayed by the control group, which supports the idea that NSS not only exist before the psychotic episode but also endure over the lifespan. Other authors have also found these mixed trait/state features (Bachmann et al., 2005). For example, neuro-motor abnormalities might be characteristic of people between infancy and middle-to-late childhood but attain a greater stability thereafter. In addition, conflicting results have also characterised studies that evaluated the relationship between psychopathological status, and its changes, and NSS after starting the drug treatment at the onset of psychosis (Browne et al., 2000; Flyckt et al., 1999; Sanders and Keshavan, 1998; Sanders et al., 1994; Scheffer, 2004; Whitty et al., 2003) and in chronic states (Bombin et al., 2005). While a possible reason for the inconsistency of these results lies in the different scale used to measure NSS, it remained to be answered whether changes on NSS might be explained only by psychopathological changes or if there was a room for the effect of drug treatment. Our results suggested that the improvement of NSS was not exclusively due to the improvement in psychopathological syndromes.

In summary, NSS were present in patients with FEP before beginning an antipsychotic treatment and improved regardless of the treatment to which they were assigned. Only a minority of patients, however, achieved a reliable and CMC. Thus, examining individual response to drug treatments using the RCI and CMC methods may complement the conventional responder/non-responder approach and pave the way for a better understanding of treatment-related changes.

Strengths and Limitations

This study has three primary strengths. First, this study is a longitudinal examination of antipsychotic-naïve patients with FEP who we followed up as outpatients. Second, we directly addressed the effect of risperidone and olanzapine as well as two other treatment regimens not usually included in clinical trials (i.e., mixed and non-medicated treatments). Third, we used the NES, the most widely employed standardized instrument, to assess NSS.

Our findings should be understood in the context of its limitations. Our results cannot be generalized to all patients with psychosis because our methodology incorporated an assessment that required cooperative patients, thereby excluding some patients (Cuesta et al., 2009). In addition, NSS improvement related to learning by practice could not be discarded because of the lack of follow up in healthy controls and because of concerns about human subjects, which prevent us to maintain the drug-naïve state in patients.

Besides, our study included a relatively high proportion of patients diagnosed of Brief psychotic disorder. This result is in contrast with prevalence rates reported for large samples comprising first-episode patients, such as for instance the McLean-Harvard International First Episode Project (Salvatore et al., 2007). In the latter study the prevalence was 7.4% with low diagnostic stability of diagnosis in the follow-up. In addition, the lifetime prevalence of BPD in a nationally representative sample was even lower (0.05%, range 0.02-0.14%) (Perala et al., 2007). This unexpected relatively high prevalence of BPD patients in our study should be taken into account regarding the generalization of our results to other samples.

Differences in symptomatic remission among treatment groups might account for by significant differences in reduction of NSS (Whitty et al., 2003). However, there not were significant differences in mean SAPS and SANS total scores among the four groups.

The discrepant results in the frontal sings subscale could be attributed to their baseline scores, which were too low to show a significant change after treatment.

Caution is warranted regarding the relatively small sample of patients in the group who did not receive treatment. Future replication of this effect in larger samples is needed.

Although the RCI is more effective at identifying reliable improvement compared to non-significant change or deteriorating outcomes (Lunnen and Ogles, 1998), note that both the RCI and CMC methods offer complementary information. They are useful clinical tools that may help psychiatrists identify patterns of recovery in patients and assist literature examinations. Moreover, they provide a method to visualize results, allowing researchers to depict individual parameters of treatment response. However, note that these methods represent only a subset

of the possible characterizations of clinical significance (Kraemer et al., 2003) and that they may be used to supplement but not to replace clinical judgment.

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CONFLICTS OF INTEREST

All authors report no conflicts of interest.

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Contributors

Manuel J. Cuesta and Victor Peralta designed the study, analysed the data and wrote the first draft of the manuscript. Maria S. Campos, Elena Garcia de Jalon, and Ana M. Sanchez-Torres managed the literature searches, collected the data and contributed to the data analysis. All authors contributed to and approved the final draft of the paper.

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Figure(s)

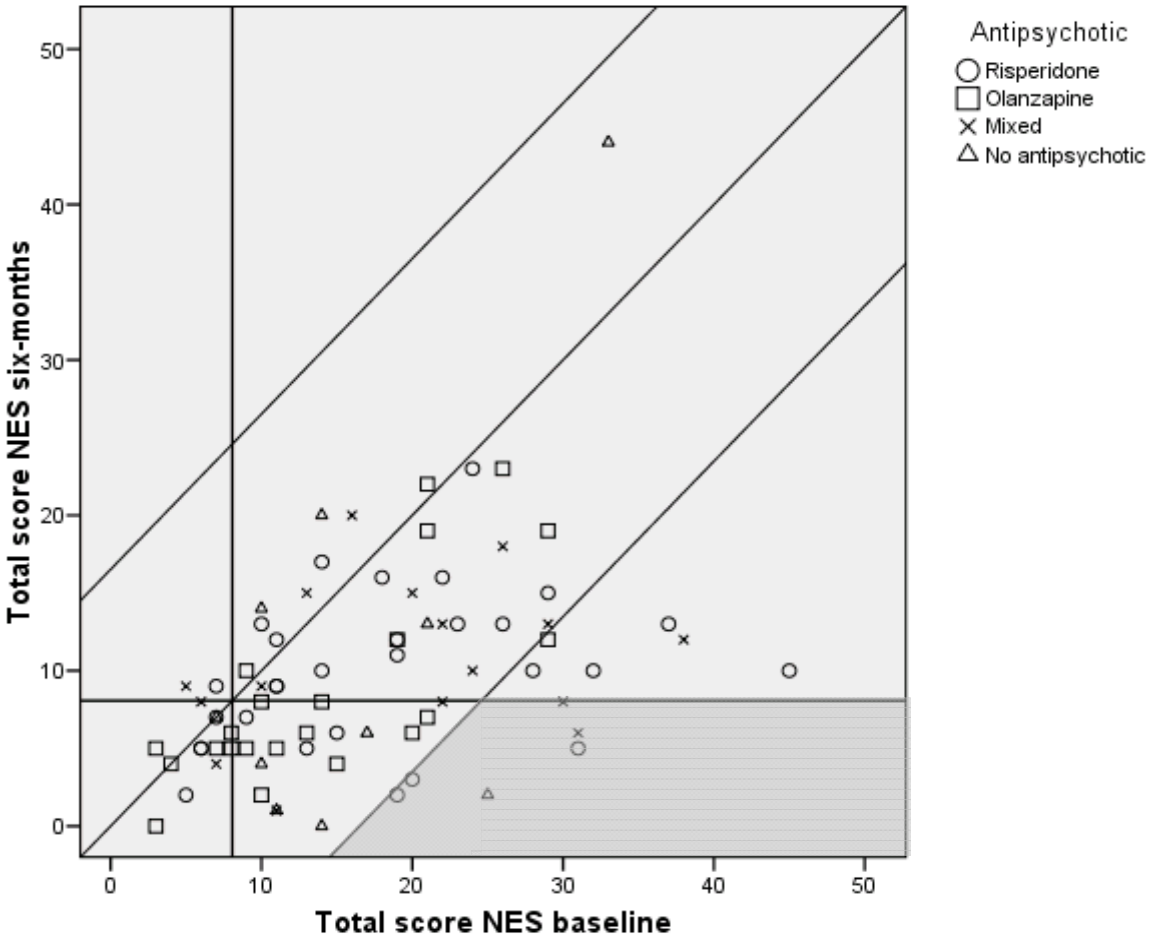

Figure 1. Longitudinal changes of NES total scores in total sample. Geometric symbols denote patients assignment treatment groups The grey area delineate those patients with both reliable and clinically significant change of the NES total score. The X-axis represents the baseline NES total score and the Y-axis is the 6-months NES total score. Patients on, above or below the diagonal line were respectively those showing no change, worsening or improving. The two parallel lines to the diagonal represent the confidence interval of RCI. Thus patients below the inferior diagonal are those showing a reliable change. Two inner x and y axes were put in order to display the C criterion. Patients in the inner quadrant x/–y were those displaying a clinically significant change; those in the inner quadrant x/y were those failing to achieve a CSC despite sufficient initial score; and those in –x/-y quadrant comprised patient who started better than the criterion for CSC.

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Table(s)

Table 1. Socio-demographic, clinical and diagnostic variables of patients and control groups

	Patients (n=77)	Controls (n=28)	Statistical analysis
Background characteristics			
Men: Women (n, %)	53 (68.8): 24 (31.2)	19 (67.9): 9 (32.1)	X^2=0.009;df=1; p=.924
Age (years ± sd)	30.09 (10)	30.64 (6.22)	t = .337; p= .737
Education (years ± sd)	13.92 (4.04)	14.29 (3.16)	t = .430; p= .668
Marital status (n, %)			
Single	67 (87)	18 (64.3)	
Married	7 (9.1)	8 (28.6)	X^2= 7.219; df=2; P=**.027**
Divorced	3 (3.9)	2 (7.1)	
Laterality (Edimburgh test)			
Right handed	69 (89.6)	26 (92.9)	
Left handed	3 (3.9)	2 (7.1)	
Ambidexterity	5 (6.5)	0 (0)	
Neurological Soft Signs			
NES and subscales (mean ± sd)			
Total score	17.05 (9.36)	5.07 (3.13)	t = 9.821; p= **.000**
Sensory integration	3.44 (2.52)	2 (1.19)	t = 3.961; p= **.000**
Motor coordination	1.58 (1.69)	0.18 (0.39)	t = 6.822; p= **.000**
Sequencing of complex motor acts	4.73 (3.55)	0.82 (1.31)	t = 8.242; p= **.000**
Frontal signs	0.31 (0.81)	0.04 (0.19)	t = 2.772;; p= **.007**
Other*	6.99 (4.39)	2.04 (1.79)	t = 8.187; p= **.000**
Diagnostic and clinical variables of patients group			
DSM–IV–TR diagnosis, n (%)			
Schizophrenia	33 (43)		
Schizoaffective disorder	6 (8)		
Brief psychotic disorder	18 (23)		
Schizophreniform disorder	12 (16)		
Delusional disorder	6 (8)		
Atypical psychosis	2 (3)		
Psychopathological scores	**SAPS Total score[a]**	**SANS Total score[b]**	
Baseline	10.09 (3.49)	8.03 (5.90)	
1-month	3.22 (3.60)	4.84 (5.11)	
6-month	1.62 (2.08)	4.74 (4.92)	

[a]Repeated measures MANOVA F= 352, 84, p≤0.001
[b]Repeated measures MANOVA F= 19.81, p≤0.001
*= Other subscale was composed of 'Others' subscale of NES without the new Frontal signs derived subscale.

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Table(s)

Table 2. Cross tabulation of RCI* against Clinically meaningful change for NES total score and NES subscales (n=77).

		Clinically meaningful change (CMC)		
		Clinically meaningful change (CMC) (%)	Started better than criterion for CMC (%)	Failed to achieve a CMC (%)
Total score NES (n, %)				
RCI	Improvement	6 (7.8)		6 (7.8)
	Stable	18 (23.4)	13 (16.9)	34 (44.1)
	Worsening			
Sensory Integration (n, %)				
RCI	Improvement	7 (9.1)		
	Stable	25 (32.5)	25 (32.5)	19 (25.0)
	Worsening			1 (1.3)
Motor Coordination (n, %)				
RCI	Improvement	6 (7.8)		3 (3.9)
	Stable	18 (23.4)	23 (29.9)	26 (33.7)
	Worsening			1 (1.3)
Sequencing of complex motor acts (n, %)				
RCI	Improvement	8 (10.4)		1 (1.3)
	Stable	19 (24.7)	16 (20.8)	33 (42.8)
	Worsening			
Frontal Signs (n, %)				
RCI	Improvement	1 (1.3)		
	Stable	6 (7.8)	53 (68.8)	14 (18.22)
	Worsening			3 (3.9)
Others Signs (n, %)				
RCI	Improvement	3 (3.9)		6 (7.8)
	Stable	18 (23.4)	8 (10.4)	42 (64.5)
	Worsening			

* RCI: Reliable Change Index

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Table(s)

Table 3. Cross tabulation of RCI* against Clinically meaningful change for NES total score and NES subscales by treatment group

		Clinically meaningful change		
		Clinically meaningful change (CMC) (%)	**Started better than criterion for CMC (%)**	**Failed to achieve a CMC (%)**
Risperidone (n= 29) (n, %)				
RCI	Improvement	3 (10.3)		4 (13.8)
	Stable	3 (10.3)	4 (13.8)	15 (51.8)
	Worsening			
Olanzapine (n= 22) (n, %)				
RCI	Improvement			1 (4.5)
	Stable	9 (40.9)	6 (27.3)	6 (27.3)
	Worsening			
Mixed (n= 16) (n, %)				
RCI	Improvement	2 (12.5)		1 (6.3)
	Stable	2 (12.5)	2 (12.5)	9 (56.2)
	Worsening			
No Antipsychotic Drug (n= 10) (n, %)				
RCI	Improvement	1 (10)		
	Stable	4 (40)	1 (10)	4 (40)
	Worsening			

* RCI: Reliable Change Index

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