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Review

On the use of the Positive and Negative Syndrome Scale in randomized clinical trials

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ABSTRACT

In the last 25 years, the Positive and Negative Syndrome Scale (PANSS) has been largely used to assess schizophrenia symptom intensity, but little information is available on how this scale was generally applied when evaluating the efficacy of schizophrenia therapies in randomized clinical trials. In the attempt to address this topic, a systematic PubMed Search was carried out using the keywords "PANSS" and "Randomized Clinical Trials". The analysis of retrieved articles highlighted that PANSS has constituted a suitable psychometric instrument to investigate the efficacy of pharmacological and non-pharmacological therapies. However, the information potentially provided by this scale was only partially reported in research articles, when characterizing the symptomatic features of patients at baseline. Furthermore, a consensus is needed to identify methodological strategies that may properly adapt PANSS-subscale structure with the symptomatic profiles of individuals enrolled in randomized controlled trials. The possibility that PANSS interview procedures and enrollment eligibility criteria may influence the symptomatic composition of patients involved in these studies is also discussed.

1. Introduction

Twenty-five years have already passed since Kay and collaborators developed the Positive and Negative Syndrome Scale (PANSS) with the purpose to provide a comprehensive and reliable instrument for assessing schizophrenia symptoms (Kay et al., 1987). The scale comprised thirty items previously included in the Brief Psychiatric Rating Scale (18 items) and in the Psychopathology Rating Scale (12 items). PANSS items were divided in three subscales (Positive, Negative and General Psychopathology subscales), starting from the hypothesis that positive and negative symptoms may constitute the main dimensions of schizophrenia (Crow, 1980; Andreasen and Olsen, 1982), and in order to provide a contextual assessment of patient general psychopathological status (Kay et al., 1987). PANSS was also combined with a semi-structured interview and detailed definitions of seven levels of symptom intensity (scores from 1 to 7) were provided for each item (Kay et al., 1987).

Preliminary studies indicated that PANSS possessed an adequate construct validity, inter-rater reliability and external validity (Kay et al., 1987). Further analyses confirmed that PANSS may constitute a suitable instrument for the assessment of schizophrenia symptoms (Kay et al., 1988, 1989), however some PANSS characteristics became a matter of discussion. Kay and collaborators indicated that a four dimensional pyramidal model could better describe the heterogeneous symptomatic features of schizophrenia (Kay and Sevy, 1990). Furthermore, PANSS-subscale structures including four, five, or six subscales have been proposed starting from the results of principal component analyses (PCAs) and confirmatory factor analyses (CFAs) (Lindenmayer et al., 1994; Peralta and Cuesta, 1994; von Knorring and Lindström, 1995; Marder et al., 1997; Van den Oord et al., 2006; Villalta-Gil et al., 2006). Recently, studies based on item response theory indicated that PANSS should be modified taking account the necessity to reduce item redundancy and response options (Khan et al., 2011; Levine et al., 2011). Furthermore, it was suggested that PANSS items should be rescaled with the assignment of score ranging from 0 to 6, so to avoid incorrect calculations when analyzing data (Leucht et al., 2010; Obermeier et al., 2010). Finally, Kay and collaborators combined the structured clinical interview for the PANSS (SCI-PANSS) (Opler and Ramirez, 1992) with the DSM-III-R Structured Clinical Interview and Rating Criteria (SCID), with the purpose to integrate the functional-dimensional assessment of PANSS into the diagnostic system of the American Psychiatric Association (Kay et al., 1991).

Beside the attempts to improve the validity and manageability of PANSS, this scale remains one of the most widely used psychometric tools to assess schizophrenia symptoms. PANSS was translated and validated in several languages (Kay et al., 1990; von Knorring and Lindström, 1992; Igarashi et al., 1998; Lançon et al., 1999) so that clinicians of different countries could use this psychometric instrument for their evaluations of schizophrenia symptoms in first-admitted patients

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and in those receiving therapies. Moreover, a variety of clinical trials adopted PANSS to evaluate the efficacy of new therapeutic strategies in controlling schizophrenia symptoms. Particularly, PANSS has been extensively used in randomized clinical trials (RTs), whose experimental design is considered highly trustable by researchers, since the occurrence of experimental bias or data misinterpretations is reduced by the randomized assignment of subjects to different experimental groups. The possibility to conjoin the reliability of RT experimental design with the completeness of PANSS was indeed regarded as an advantageous approach for a proper assessment of the efficacy of schizophrenia therapies.

In spite of the large use of PANSS, there is still little information on how this scale was generally applied in RTs. It is unclear which of the proposed modifications of PANSS have been accepted by researchers, and whether the large amount of quantitative and qualitative information potentially provided by PANSS was generally reported in research articles. Finally, there is no global data depicting the symptomatic characteristics of patients involved in RTs using PANSS (PANSS-RTs) to assess schizophrenia symptom intensity.

In the attempt to collect information on the use of PANSS in RTs, the present analysis reviewed the available scientific literature, focusing on (i) how PANSS results are depicted within research articles; (ii) the PANSS subscales mostly used in RTs; and (iii) the demographic and symptomatic characteristics of individuals enrolled in PANSS-RTs.

2. Methods

2.1. Data source and inclusion criteria

A systematic PubMed advanced search of PANSS-RT articles was carried out using the keywords "PANSS" and "Randomized Clinical Trial". All English written research articles reporting PANSS-RTs published between 1987 and 2012 were collected, but only PANSS-RT articles showing original data (*o*-PANSS-RT articles) were included in the analysis, so to avoid overestimation when evaluating the characteristics of patients enrolled in PANSS-RTs.

The therapeutic area of interest of all *o*-PANSS-RTs was recorded, then the articles were divided in two groups: i) *o*-PANSS-RT articles showing complete PANSS data (*C*-PANSS-RTs); and ii) *o*-PANSS-RT articles providing incomplete PANSS data (*Inc*-PANSS-RTs). An article was considered *C*-PANSS-RT when it reported the number of examined patients (n) and the scores (mean ± SD or mean ± S.E.M.) of all PANSS subscales and PANSS total at baseline.

From *Inc*-PANSS-RTs, the percentage of articles missing on one of the above mentioned data was calculated. *C*-PANSS-RT articles were reviewed to identify the PANSS subscales and interviews mostly used in PANSS-RTs. Furthermore, the country where the study was carried out, and whether authors defined the study as a multicenter trial were recorded.

2.2. Sample composition in PANSS-RTs

Baseline demographic and symptomatic characteristics of individuals enrolled in PANSS-RTs were collected from *C*-PANSS-RTs adopting the three-factor model or the five subscales (positive, negative, disorganized thoughts, uncontrolled hostility and anxiety/depression subscales) developed by Kay et al. (1987) and Marder et al. (1997), respectively. Eligibility criteria for patients to be enrolled in these studies were recorded and categorized in the following groups: age, symptom intensity, inability to provide consensus/uncooperativeness, general clinical status, abuse of substances, other. Furthermore, the number of *C*-PANSS-RTs requiring minimal symptom levels for eligibility that could match with Andreasen remission criteria (i.e., item-score ≤ 3 in P1, P2, P3, N1, N4, N6, G5, and G9, for at least 6 months) was verified (Andreasen et al., 2005).

Baseline PANSS scores were recorded from *C*-PANSS-RT articles showing data as numerical values. The distribution of mean baseline PANSS scores obtained from different studies was estimated collecting data of *C*-PANSS-RTs adopting Kay three-factor structure, since the number of retrieved articles allowed an appropriate percentile subdivision of average scores and variability analyses. The weighted mean, SD and confidence intervals (CI) of baseline PANSS scores of the population of patients enrolled in PANSS-RTs were calculated from *C*-PANSS-RTs adopting the Kay three-factor structure and Marder five-subscale model, separately.

3. Results

3.1. Retrieved PANSS-RT articles

The PubMed search retrieved 526 articles and, among them, 363 articles (69%) were selected as *o*-PANSS-RTs. The number of *o*-PANSS-RT articles strongly increased from 1994, while fluctuations could be observed starting from 2007 (Fig. 1). More than half of *o*-PANSS-RTs evaluated the clinical efficacy of antipsychotic drugs, but an increasing amount of research articles focused on other therapeutic approaches, such as psychological interventions, nutraceutical/plant-extract/hormone and Transcranial Magnetic Stimulation (TMS) administrations (Table 1). Albeit, the efficacy of new therapeutic strategies was often tested in patients undergoing a pharmacological treatment, only 9.4% of *o*-PANSS-RTs specifically investigated the effects induced by two well defined combined therapies (Table 1). A further 21% of *o*-PANSS-

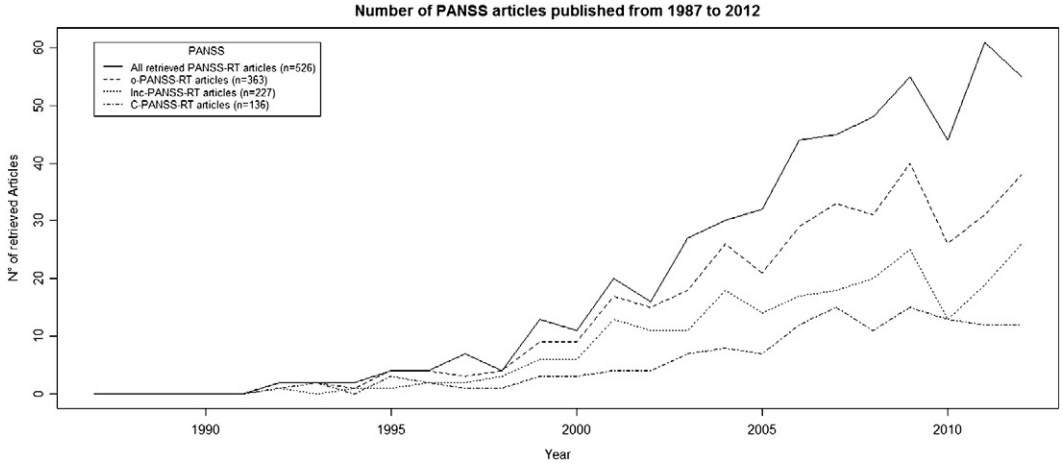

Fig. 1. Graph showing the number of PANSS articles published from 1987 to 2012. English written articles were retrieved from a systematic PubMed search and using the keywords "PANSS" and "Randomized Clinical Trial".