Available online at www.sciencedirect.com
ScienceDirect
Schizophrenia Research 98 (2008) 318–322
SCHIZOPHRENIA RESEARCH
www.elsevier.com/locate/schres

Extrapolation between measures of symptom severity and change: An examination of the PANSS and CGI

Stephen Z. Levine [a,*], Jonathan Rabinowitz [a], Rolf Engel [b], Eva Etschel [b], Stefan Leucht [c]

[a] Bar Ilan University, Ramat Gan 52900, Israel
[b] Psychiatrische Klinik der Ludwig—Maximilian—Universität München, Nussbaumstrasse 7, 80336 München, Germany
[c] Klinik für Psychiatrie und Psychotherapie der TU—München, Klinikum rechts der Isar, Ismaningerstr. 22, 81675 Muenchen, Germany

Received 14 June 2007; received in revised form 14 August 2007; accepted 6 September 2007
Available online 18 October 2007

Abstract

Objective: Research based on pooling data from clinical trials suggests that it is possible to extrapolate from a CGI-S to a PANSS severity score and from the CGI-I to a PANSS percentage change score. This research has not been replicated nor examined in individual trials. This study aims to examine the feasibility of extrapolation from the CGI to the PANSS across and within 4 large clinical trials of antipsychotic medication.
Methods: Equipercentile linking is used to examine extrapolation (a) from CGI-S to PANSS severity ratings and (b) from CGI-I to PANSS percentage change ($n=2698$). Linking is conducted at baseline and after 2, 4, 6 and 8 weeks of treatment from ITT clinical trial participants with schizophrenia.
Results: Across weeks 2, 4, 6 and 8, being considered 'not ill' according to the CGI-S corresponded to PANSS scores of 31–2. The relationship between the CGI-S and the PANSS followed an increasing trend, such that 'very mild' corresponded with 41–7, 'mild' corresponded with 55–62, 'moderate' corresponded with 71–7, 'marked' corresponded with 88–94, 'severe' corresponded with 105–110, and 'extremely severe' corresponded with 126–134. The relationship between CGI-I ratings and percentage change followed a linear trend, such that 'very much improved' corresponded to PANSS percentage change scores from 79 to 75, 'much improved' corresponded with 45 to 49, 'minimally improved' corresponded with 21 to 23, 'unchanged' corresponded with 2 to 3, 'minimally worse' corresponded with −15 to −20, 'much worse' corresponded with −44 to −51. Generally, within the trials the cut-off ranges identified overlapped within around 10 points of those found in the pooled analysis.
Conclusions: Despite trial heterogeneity, the results support the extrapolation from the CGI-I to PANSS percentage change. Extrapolation of the CGI-S to the PANSS is observed, except in the case of severe symptomatology which is rare. Collectively, the results support the extrapolation between the PANSS and CGI.

Keywords: Schizophrenia; Severity of illness index; Treatment outcome

1. Introduction

Two of the most widely used measures of treatment efficacy in clinical trials of antipsychotic medications are the Positive and Negative Symptoms Scale (PANSS) and the Clinical Global Impression Scale (CGI). The PANSS aims to provide a comprehensive measure of symptomatology (Kay, 1990; Kay et al., 1987, 1989). It consists of 18 items from the Brief Psychiatric Rating Scale (Overall and Gorham, 1962) measuring positive symptoms, general psychopathology and affective symptoms, and

* Corresponding author.
E-mail address: levins@biu.ac.il (S.Z. Levine).

0920-9964/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2007.09.006

12 items from the psychopathology rating schedule (Singh and Kay, 1975). Together these form 7 items to measure positive symptoms, 7 items to measure negative symptoms and 16 items to measure general psychopathology. The PANSS items are frequently summed to provide a general index of symptom severity (Kay et al., 1987). The CGI (Guy, 1970) has two versions each consisting of one item on a seven point scale that is rated by symptom severity or change. Therefore, the CGI provides an overall index of symptom severity or change. Thus while the PANSS is more comprehensive, the CGI may be more practical to administer. Also, the CGI is easier to use and understand, although the PANSS may be preferred due to its strong psychometric properties of reliability and validity (Reviewed in Kay et al., 2000). The clinical implications of the PANSS, however, are sometimes not readily apparent (Leucht et al., 2006). For instance, it is difficult to provide a clinical judgment based on a PANSS total score of 50 or 70. Similarly, PANSS change scores range from 20% to 50% (e.g., Leucht et al., 2006). The use of the PANSS in this way assists in the definition of "response", but what these cut-offs mean from a global "clinical" perspective is unclear. The CGI, however, is a frequently used instrument that appears to be more informative in this regard. It describes a patient's overall clinical state as a global impression by the rater. It therefore provides more readily understood clinical information than the PANSS which has more desirable psychometric features. This research is informative to clinicians since it explains the relationship between the PANSS (a widely used 30 item research instrument of symptom severity) with global ratings that are easily understood (i.e., the CGI).

This makes it desirable to extrapolate from the CGI to the PANSS. Past research based on pooling data from clinical trials indicates that it is possible to extrapolate from the CGI to the PANSS (Leucht et al., 2005b). For instance, past research over a 6 week period indicates that a CGI rating of mildly ill corresponds to a PANSS total of 58 at baseline. A minimal improvement according to the CGI corresponds to a PANSS mean percentage reduction of 19% after 1 week, a figure that increases during the course of a trial. The purpose of the current study is to examine the extrapolation between CGI and PANSS severity or change across and within individual clinical trials of antipsychotic medication over an 8 week period.

2. Methods

PANSS and CGI data on 2698 persons were extracted and examined from four randomized controlled clinical trials of antipsychotic medication used to treat schizophrenia. These included: INT-2, $n=1362$ (Peuskens, 1995) which compared risperidone to haloperidol; INT-3, $n=520$ (Marder and Meibach, 1994) which compared risperidone, haloperidol and placebo; USA-121, $n=283$ (Kane et al., 2003) which compared long acting injectable risperidone to placebo; and INT-35, $n=533$ (Schooler et al., 2005) which compared haloperidol to risperidone. Data collected at baseline, and weeks 2, 4, 6, and 8 were examined. There were a total of 533 first episode patients (INT-35), 1362 chronic patients (INT-2) and 803 acute patients (INT-3, USA-121). All had a diagnosis of schizophrenia except the first onset patients (INT-35; $n=533$) of whom 6.7% had a schizoaffective diagnosis, and 27.9% were diagnosed with schizophreniform disorder. Two trials were international (INT-2, INT-35) and 2 were based in North America (USA-121, INT-3) (for further details see Rabinowitz et al., 2006). In these respects, the trials appeared to be fairly heterogeneous. All treatment groups in the studies were included to maximize generalizability, as previously (Leucht et al., 2005b; Rabinowitz et al., 2006).

2.1. Analytic approach

To examine the extent to which it is possible to extrapolate from the CGI to the PANSS we conducted equipercentile linking. This is defined as 'a statistical process that is used to adjust scores on test forms so that scores on the forms can be used interchangeably' (Kolen and Brennan, 2004). The method has been used before in psychiatry (Leucht et al., 2006, 2005a,b) and psychology (Jensen et al., 1988) since, unlike linear regression, equipercentile linking does not assume linearity, aims to concord rather than predict, and thus provides comparable scores. In the current study we link the CGI-severity score and the PANSS total score, and the CGI-improvement score and the percentage PANSS change from baseline. Missing data were removed at each point in time.

3. Results

3.1. CGI–PANSS correlations

Spearman correlation coefficients between CGI-S and the PANSS were $r=.61$ ($n=2621$) at baseline, $r=.68$ at week 2 ($n=2432$), $r=.71$ at week 4 ($n=2227$), week 6 $r=.72$ ($n=2001$), and $r=.73$ at week 8 ($n=1810$). This pattern indicated that the correlation between CGI-S and the PANSS increased with time and repeated testing. The correlations between PANSS percentage change and the CGI were on weeks 2 through 8: .61, .67, .67 and .68, respectively (all correlations, $p<.001$).