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A Reliable Change Index to Inform Development of a Minimally Clinically Important Difference in Treatment Resistant Schizophrenia

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Background

Randomized controlled trials (RCT) are increasingly evaluated for clinical or “real world” importance. Traditionally, a 20% improvement in Positive and Negative Syndrome Scale (PANSS) score has been used to denote meaningful change in symptoms for schizophrenia.

More recently, an absolute increase of ≥12 points in total PANSS score was posited to suggest clinically important relapse in schizophrenia (Siafis *et al.,* 2024).

Justification

There is ongoing debate on how to define clinically meaningful change in symptoms.

The reliable change index (RCI) is a criterion used to determine if change in a person’s score over time is statistically significant (Zumbo *et al*., 2014). It incorporates assessment of rating reliability into evaluating change (Jacobson & Truax, 1991) and represents a ratio of actual observed difference in score between two measurements, and the standard error of measurement of the difference. As such, a RCI helps indicate whether a change in score is statistically significantly greater than a difference occurring due to random measurement error alone (Zumbo *et al*., 2014).

Objectives

To continue work in defining criteria for meaningful change in treatment resistant schizophrenia (TRS), our objectives were to

1. Quantify a RCI for total PANSS score
2. Explore application to hospitalized patients
3. Compare findings with the original study of clozapine in TRS (Kane *et al.,* 1986).

Methods

Using data from 68 participants from the Clozapine and Risperidone Enhancement (CARE) study (Honer *et al.,* 2006), PANSS ratings on day 1 and 7 (both under stable clozapine monotherapy) were used to calculate reliability using intraclass correlation, and derive a RCI for total PANSS score, and for PANSS-derived Brief Psychiatric Rating Scale (BPRS) total score (Evans *et al*.,1998).

Patients hospitalized with TRS at the British Columbia Psychosis Program (BCPP, n=355) were included in an exploratory analysis.

Mean patient age was 38 years and 26% were of female sex. PANSS scores were rated at times of admission, and discharge (median length of stay of 5 months).

Results

CARE study total PANSS scores were 97.3 (SD 13.5) and 97.0 (SD 13.2) on days 1 and 7 respectively, with an intraclass correlation coefficient of 0.90 allowing calculation of an RCI of 11.8. Using the same data, an RCI for a PANSS-derived BPRS total score was determined to be 5.8.

Table 1

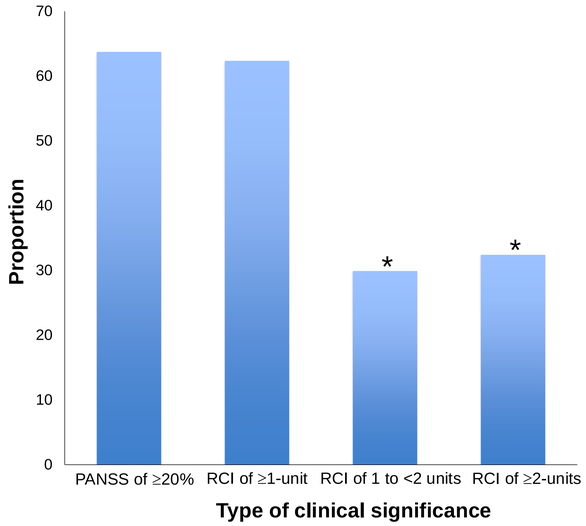
Mean PANSS scores at different times in the BCPP, including mean change from admission to discharge.

Timepoint	Mean PANSS score
Admission	95.1 (SD 18.9)
Discharge	76.8 (SD 19.6)
Change from admission to discharge	18.4 (27% change)

Results

Figure 1

Comparisons of proportion of BCPP patients having different levels of RCI compared to a PANSS of ≥20%. * *Denotes p-value <0.001, obtained using McNemar test.*



In the pivotal RCT of clozapine for TRS, total BPRS score at study entry was 61, declining to 45 for clozapine-treated and 56 for chlorpromazine-treated patients.

Using our PANSS-derived BPRS RCI of 5.8, mean changes represent 2.8-RCI units for clozapine, and 1.0 units for chlorpromazine. Interestingly, 30% of clozapine-treated patients were categorized as improved, similar to the 32% of BCPP patients achieving an RCI unit-change of 2 or more at discharge.

Discussion

The RCI for TRS in this analysis, a reduction of 11.8 total PANSS points, is remarkably similar to the 12-point increase in PANSS found to suggest illness relapse (Siafis *et al*., 2024).

Comparing our data to the original Kane *et al.,* (1986) RCT, an improvement of 1-RCI unit was associated with chlorpromazine treatment compared with 2.8 units for clozapine.

Conclusions

A change of at least 2-RCI units (23.6 points), well over 20% change in PANSS, may be needed to incorporate a clinically relevant RCI into developing an MCID for TRS.

Next Steps

We are conducting ongoing analyses of changes in day-to-day function in hospitalized TRS patients with the aim of trying to incorporate a RCI approach into an acceptable MCID for clinical trial evaluation.

References / Bibliography

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