Psychometric Validation of a Novel PRO MEASURE for Assessing Patient-reported Experience of Cognitive Impairment in Schizophrenia (PRECIS)

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Abstract

Background Cognitive impairment associated with schizophrenia (CIAS) can be a distressing feature that contributes to the burden of the disorder, as well as being a strong predictor of functional impairment. To fully assess the burden to patients living with this illness, there is a need to develop a specific measure of patient-reported outcomes . Methods Following initial development of the Patient-Reported Experience of Cognitive Impairment in Schizophrenia (PRECIS) instrument, the domain structure, reliability (inter-item consistency and test–retest reliability), and validity (discriminant validity, divergent, and convergent validity) of the tool were assessed in patients (aged 18–55 years) with CIAS participating in a 12-week, Phase II, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of BI 409306. Healthy control subjects were recruited separately. The PRECIS instrument was completed at baseline, Week 6, Week 9, and Week 12. Results The questionnaire responses of 410 patients with schizophrenia and 88 control subjects were compared. Of the original 35 items included in the draft PRECIS instrument, 11 were eliminated due to poor performance against pre-defined criteria, resulting in a 24-item questionnaire that loaded well onto 5 domains (Attention, Memory, Executive Function, Communication, and Bother). The revised 24-item PRECIS instrument demonstrated adequate discriminant validity between patient and control groups in each of the 5 domains ($p<0.0001$), convergent validity as shown by a significant correlation between PRECIS scores and the Schizophrenia Cognition Rating Scale ($p<0.0001$), good internal consistency (Cronbach's alpha score: 0.942), and adequate test–retest reliability (intra-class correlation coefficient [ICC]: 0.78). A simplified, user-friendly scoring method was identified, which assigned scores to each of the 5 domains using a five-category Likert scale. PRECIS did not correlate with MATRICS or CANTAB composite scores. Conclusions PRECIS is a novel self-completed sensitive instrument designed to measure the subjective experience of cognitive impairment in patients with schizophrenia. The test development process included patient input, perceptions, and feedback, and strong evidence for the validity and reliability of the instrument was demonstrated. The scale provides a patient-based perspective to complement existing objective measures of cognition and serves to define key patient-based endpoints for use in future clinical studies.

Background

The majority of patients with schizophrenia experience some level of underlying cognitive impairment [1]. Cognitive impairment associated with schizophrenia (CIAS), a serious and often distressing feature of schizophrenia [2], can manifest as deficits in processing speed, attention, episodic memory, working memory, social cognition, and executive function [3, 4]. As such, CIAS is associated with substantial functional impairment [2, 5], with 20%–60% of variation in functional outcome attributed to cognitive performance [2]. Patients often have some degree of awareness of cognitive deficits, but clinicians typically neglect to ask about the impact of these symptoms on the patient. Pharmaceutical management of schizophrenia has largely targeted managing positive symptoms, increasing the length of remission, and reducing the duration and severity of acute psychosis. While therapies are effective in reducing psychosis, there is typically little improvement in a patient's status, in part due to a lack of treatment effect on negative symptoms and CIAS [6]. Several performance-based instruments exist to objectively evaluate specific aspects of functional capacity and cognitive functioning, including the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) test battery [10], the Cambridge Neuropsychological Test Automated Battery (CANTAB) [11], and CogState [12]. Additionally, the clinician-rated interview-based Measure of Insight into

Cognition—Clinician Rated (MIC-CR), assesses patients' ability to verbalize their relative cognitive status focusing on attention, memory, and problem solving [Medalia and Thysen 2008]. However, given the increasing demand from regulatory bodies and health technology appraisals to increase patient-centered outcomes research including the use of patient-reported outcome (PRO) instruments [8] there is a need to capture the patients' perceptions of CIAS. Although the Schizophrenia Cognition Rating Scale (SCoRS) [9], the Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS) [13], and the Self-Assessment Scale of Cognitive Complaints in Schizophrenia (SASCCS) [14], subjectively evaluate patients' perception of CIAS, they are not without limitations. SCoRS includes modified items from dementia rating scales and therefore in not CIAS specific. The SSTICS is, by design, brief while the SASCCS was developed without patient input. Therefore, the development of a PRO instrument specific to CIAS is necessary to enable improved evaluation of new therapies in patients with schizophrenia.

This study outlines the continuing development and validation of a novel PRO instrument for assessing patient experience of CIAS, the Patient-Reported Experience of Cognitive Impairment in Schizophrenia (PRECIS). The purpose of developing this instrument was to assess the distress or difficulty experienced from impaired cognition and to detect treatment responsiveness in a clinical trial setting. The initial development and concept elicitation data for the PRECIS instrument have previously been reported [15], and development was conducted in accordance with guidance from the US Food and Drug Administration [8, 16] and the American Educational Research Association's Standards for Educational and Psychological Testing [17]. During this development, a conceptual model was proposed based on published data, clinical experience, and advice from leading clinician-scientists in schizophrenia research and neuropsychology [15]. The model included seven domains reported to contribute to the subjective experience of CIAS: attention, communication/social cognition, executive functioning, intermittent impaired perception, memory, metacognitive abilities, and sharpness of thought. Using this conceptual model, intensive concept elicitation interviews were conducted in 80 patients with schizophrenia, and an initial pool of 53 items was developed. Cognitive debriefing interviews resulted in the removal of 18 items and modification of 22 other items. The remaining 35 items represented 23 concepts within six domains plus two items assessing bother.

The instructions for the instrument were modified to include additional explanation regarding the differences between cognitive difficulties and positive symptoms, based on patient feedback [15]. The qualitative findings in these patients informed the basis of a 35-item version of the PRECIS instrument, covering 5 domains (Additional Figure A1). Two domains (sharpness of thought, intermittent, impaired perception) were omitted as having insufficient content validity or being poorly comprehended among participants. This study aimed to investigate the psychometric properties of the 35-item instrument and develop a sensitive and reliable tool for assessing patient experience in CIAS, the PRECIS. Here we report on the domain structure, discriminant (known groups) validity testing, domain scoring, and internal reliability, to assess whether PRECIS was sensitive to between-group differences, by comparing patients with schizophrenia and control subjects.

Methods

Study Design

This psychometric validation study included patients with schizophrenia who were participating in a Phase II, randomized, double-blinded, placebo-controlled, parallel group study to evaluate the efficacy (cognition and

everyday living skills), safety, and tolerability of four orally administered doses of BI 409306 during a 12-week treatment period (clinicaltrials.gov: NCT02281773) [18]. Healthy individuals (control group) were recruited separately from subgroups at the same study sites, but using a separate, parallel-study protocol (Clinicaltrial.gov: NCT01505894). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki [19], International Council for Good Clinical Practice [20], and applicable country-specific regulatory requirements. It was reviewed by the New England Research Institute's institutional review board (IRB) and each study site received individual IRB approval via Alpha IRB.

Patients

All patients/individuals were 18–55 years of age. The patient group had a diagnosis of schizophrenia (as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) and had received stable antipsychotic treatment for ≥8 weeks prior to randomization. Patients had no more than a "moderate" severity rating on hallucinations and delusions (Positive and Negative Syndrome Scale [PANSS]) and no more than "moderate" depression scores (PANSS general psychopathology syndrome depression item). The control group were free of major psychiatric illness, neuropsychological impairment and history of antipsychotic drug use. All patients, or their legally accepted representatives, provided written informed consent.

Assessments

The patient group completed the PRECIS instrument at baseline (randomization or Visit 2), Visit 4 at 6 weeks, Visit 5 at 9 weeks, and end of treatment (EOT) visit at 12 weeks. The PRECIS instrument was initially comprised of 35 items answered via a five-category Likert scale (ie, 1=not at all/not at all hard, 2=a little bit/a little bit hard, 3=somewhat/somewhat hard, 4=quite a bit/quite hard, 5=very much/very hard) [15].

Identification of an appropriate algorithm to convert the responses into numerical values was carried out once the final structure of the PRECIS instrument was determined, as described below. In addition to the PRECIS instrument, the CANTAB and the MATRICS Consensus Cognitive Battery (MCCB) were used to objectively assess cognitive function. The SCoRS was conducted to subjectively assess cognitive impairment. Patients completed the CANTAB and MCCB during Screening, Visits 2 and 4, and EOT. The SCoRS was completed at Visit 2 and EOT. The control group completed the original 35-item PRECIS instrument, the MCCB, CANTAB, and SCoRS at a single visit.

Statistical Analyses

Analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, CA, USA). Descriptive statistics were calculated for demographic variables (age, gender, race, and ethnicity). For individual items in the PRECIS instrument, the mean, standard deviation (SD), range, and ceiling and floor effects were calculated. Effects of gender (female vs male), age (≤45 years vs >45 years) and race-ethnicity (white vs black vs other) on PRECIS item scores (35-item instrument) were examined using standard statistical tests.

Responses to the PRECIS instrument were converted into a total score (unweighted), calculated using the sum of the 35-item scores divided by 35 (average item score). Individual domain scores (scores for each category of items) were computed as the average score across all items within each domain. Any data points missing ≥10% of data were excluded. If more than one item was missing from a domain, the domain score for the patient was

excluded. Individual items with less than adequate reliability or validity were identified and eliminated or modified. Items that met the following pre-defined elimination criteria were considered poorly performing and were considered for elimination from the 35-item instrument:

- floor or ceiling effects of >50% among patients
- ≥10% missing data
- relatively low factor loadings across the domains (<0.025)
- Cronbach alpha inflation of >10% above the original value upon item removal
- lower internal or test–retest reliability (≤6)
- failure to distinguish statistically between patients and controls in discriminatory validity testing (statistical cut-off: p=0.05).

Analyses were repeated on the revised instrument once poorly performing items were removed. Item finalization was performed over two rounds of analysis and alternative scoring procedures were considered.

Factor Analysis

An exploratory factor analysis (EFA) was conducted to determine the dimensionality of the latent variables (ie, domains) being assessed by the 35-item PRECIS instrument and to identify common factors (domains) among the 35 items. All pre-treatment scores in the patient group, and for patients and controls combined, were used for these analyses. The control group (N=88) had insufficient sample size for a separate factor analysis. The number of derived factors was based on eigenvalues (threshold of >1.0), a scree test, and the interpretation of simple structure. Both Promax and Varimax rotations were employed to identify correlated factors and uncorrelated factors, respectively, to evaluate the strength of domains. A preliminary confirmatory factor analysis (CFA) was carried out after the poorly performing items had been eliminated and a 24-item version of the PRECIS instrument was available for testing.

Reliability

Reliability was assessed using assessments of internal reliability and test–retest replicability. Internal reliability, or inter-item consistency, of the original 35-item PRECIS instrument was evaluated by means of Cronbach's alpha [21, 22] based on data obtained at baseline from patients with schizophrenia. Cronbach's alpha ranges from 0 to 1, with higher values indicating increased reliability. Inter-item correlations were analyzed using Spearman's (non-parametric) rank order correlation coefficients. Unfortunately, repeated administrations of the PRECIS items during the pre-treatment or run-in phase of the study, as would ideally be used for test–retest purposes, were not included during the main clinical trial (NCT02281773). These analyses were therefore performed during the last phase of the clinical trial (Weeks 9–12). Intra-class correlation coefficients (ICCs) were used to analyze test–retest reliability of the responses to the 35 individual PRECIS items between Visit 5 (Week 9) and EOT (Week 12). To control for potential treatment-related changes associated with the active drug condition, we included only subjects in the placebo condition, who also had stable composite CANTAB scores during this final study period (defined as >1-point change in either direction) between the last two study visits.

As patients had been randomized to receive treatment that may have influenced their cognitive impairment, this potentially reduced the reliability of the test–retest analysis. To minimize this variability, test–retest analyses

were conducted in a subset of placebo-treated patients with stable CANTAB scores (defined as <1-point change in either direction). ICCs, percent agreement scores and paired *t*-test comparisons of scores were calculated to compare PRECIS instrument responses at Visit 5 and EOT. Correlations of ≥0.70 were defined as good reliability [23]. This analysis was repeated for the revised PRECIS total and factor scores, once poorly performing items had been eliminated.

Validity

For both the original 35-item and the subsequent 24-item versions of the PRECIS instrument, discriminant validity assessed whether it was possible to differentiate between the patient and control groups. PRECIS responses from both groups recorded at randomization were compared using an exact Wilcoxon two sample (non-parametric) test. Convergent and divergent validity were assessed by correlating pre-randomization PRECIS scores with related and unrelated domains from other validated instruments (CANTAB, MCCB, and SCORS), using Spearman's (non-parametric) rank order correlation coefficients for patients with schizophrenia. Strong and poor convergent validity was defined as correlations of ≥0.70 or ≤0.40, respectively. These analyses were repeated on the revised, 24-item PRECIS instrument to ensure its validity.

Results

Baseline Characteristics

A total of 410 patients with schizophrenia and 88 healthy individuals were enrolled. Overall, the patient group was older than the control group (mean [SD]; patient group, 43.0 [9.5] years; control group, 33.2 [11.1] years), and included a larger percentage of males and African Americans (Table 1).

Effects of gender, age, and race-ethnicity on PRECIS item scores were examined, revealing that none of the item scores were affected by gender or age, and few differences were observed based on race-ethnicity of the participant. Therefore, the potential effects of these demographic variables were not analyzed further.

Item Elimination and Development of a Revised PRECIS Instrument

Item response distributions, EFA, reliability and validity of the 35-item PRECIS were assessed initially. Results from these analyses are described in Additional File 1, Additional Figures A2 and A3, and Additional Tables A1 and A2.

Items that met the pre-determined criteria were eliminated from the 35-item PRECIS instrument. Two of the 35 items poorly loaded onto the identified domains with a Varimax correlation <0.50. Marked floor effects in patient groups resulted in the elimination of 5 further items. Regarding test–retest reliability, 3 items scored <50% between visits, leading to their elimination from the revised instrument. A further item (CIAS #112) was found to be significantly different between visits and was also eliminated (Additional Table A3). No items were eliminated due to inadequate inter-item consistency or lack of discriminant validity. Analysis of the 35-item PRECIS instrument therefore resulted in elimination of 11 items, in accordance with the pre-defined elimination or inclusion criteria (Additional Table A3). The revised PRECIS instrument included 24 items, which were also assessed (Additional Table A4).

Analysis of Revised 24-item PRECIS Instrument

Factor Analysis

Of the remaining 24 items in the revised PRECIS instrument, 22 function items were subjected to preliminary CFA. The two “Bother” items were excluded from the preliminary CFA for conceptual reasons, as they were designed to assess the degree to which the rest of the scale mattered to the patient. All subsequent analyses (validity, reliability, and scoring algorithm assessment) utilized the five-domain (24 item) instrument. The preliminary CFA identified one strong factor (Attention; eigenvalue: 9.74) and 3 additional factors (Memory, Executive function and communication; eigenvalues: 1.10–1.52; Table 2, Additional Table A5, Additional Figure A4). Similar factor solutions were calculated using Varimax (Table 2) and Promax (data not shown) rotations. Re-insertion of the “Bother” factor, resulted in a final five-factor solution.

Reliability

There was a high level of internal consistency both for the overall 24-item PRECIS instrument (Cronbach’s alpha score of 0.942) and individual domains (Cronbach’s alpha scores: 0.743–0.873; Table 3). The Cronbach’s alpha score for the 24-item instrument was compared with the resulting score following removal of each of the items in turn, to confirm that no individual item was decreasing the overall reliability of the score. Individual item correlations within each of the subscales showed adequate or better internal consistency for individual items and domains, in addition to the overall PRECIS score (Table 3).

For the revised 24-item PRECIS instrument, test–retest analysis for the 5 domains, as shown by ICC in 111 patients, ranged from 0.49 to 0.74, with moderate–high levels of agreement across testing visits (60.4%–74.8% agreement; Table 3). An outlier ICC value <0.50 was noted for the communication domain, which nevertheless had a high (62.2%) agreement ratio, in keeping with the other domains. As this scale was revised, item-level ICC and percentage agreement analyses were not conducted to avoid duplicating domain analyses (Table 3). Overall, the ICC for the total 24-item PRECIS instrument in test–retest analysis was 0.78, with 73% agreement between responses of patients over two separate visits.

Validity

Discriminant validity testing confirmed there were significant differences between the patient and control groups in each of the 5 domains in the revised 24-item PRECIS instrument (p<0.0001; Table 4). Convergent validity was demonstrated through a significant correlation between PRECIS total and individual domain scores with the SCoRS global rating scale (p<0.0001). There was no correlation between the PRECIS instrument and CANTAB composite or domain scores, with the exception of Verbal Recall/Recognition Memory, which correlated with Domain 2 (Memory) of the PRECIS instrument (Table 5). There was no correlation between the PRECIS instrument total and MCCB composite scores; however, MCCB composite score was correlated with Domain 3 (Executive Function) of the PRECIS instrument (p=0.03). (Table 5). For the MCCB domain scores, there were statistically significant correlations between Domain 2 (Memory) of the PRECIS instrument and the MCCB domains of Attention/Vigilance (p=0.03) and Working Memory (p=0.01). Likewise, Domain 3 (Executive Function) of the PRECIS instrument was also significantly correlated with the Attention/Vigilance (p=0.05) and Working Memory (p=0.01) domains of the MCCB.

Proposed Scoring Algorithm

For the revised five-domain model and 24-item version of the PRECIS instrument, a simplified, user-friendly scoring method was identified that assigned scores to each of the 5 domains (Attention, Memory, Executive Function, Communication, and Bother). Using this method, the five-category Likert scale is converted into numerical values (1–5). Domain scores equal the sum of the individual item scores divided by the number of items within the domain, ie, the average of all items within the domain. An unweighted total score can then be calculated using the sum of the first 22 item scores divided by 22 (ie, the average item score), providing >90% of the items in the scale or subscale are answered. The unweighted score does not include the two items of Bother as these items apply to all domains.

Discussion

This study aimed to develop and validate a sensitive and reliable PRO instrument for assessing patient experience in CIAS, according to US Food and Drug Administration guidelines [8, 16]. This well-powered, clinical psychometric validation study demonstrated that the revised 24-item version of the PRECIS instrument has adequate discriminant validity, good internal consistency, adequate test–retest reliability, and good-to-excellent intra- and inter-item correlations, providing strong evidence of its validity and reliability. The PRECIS instrument also demonstrated good convergent validity, based on correlations with the SCoRS. Moreover, there were very few correlations between the PRECIS instrument and the CANTAB or MATRICS test battery domain and total scores, which further demonstrates the specificity of PRECIS in assessing patients' personal experiences of cognitive impairment. Such experiences can be independent of objective cognitive impairments assessed using performance-based measures (eg, CANTAB and MATRICS test battery) [24, 25]. The PRECIS and SCoRS instruments differ in their methodology, in that they involve patient-reported and clinician/observer-reported outcomes, respectively. However, the correlation between the two instruments is consistent with the notion that PRECIS may measure the effect of CIAS on patients' day-to-day functioning, rather than being a direct measurement of cognitive impairment. Overall, the PRECIS instrument is a novel PRO tool with strong evidence of validity and reliability, designed using patient feedback to measure the subjective experience of CIAS.

Based on the psychometric data and iterations of factor analysis explored in the study, the original 35-item PRECIS instrument has been reduced to 24 items across 5 domains (Attention, Memory, Communication, Executive Function, and Bother). Overall, the preliminary CFA of the 24-item PRECIS instrument confirmed the original conceptual model of 5 domains (Attention, Memory, Communication, Executive Function, and Bother; Figure A1); however, a disparity in eigenvalues between the Attention domain (eigenvalue: 9.74) and the domains of Memory, Communication, and Executive Function (eigenvalues: 1–2) was observed. The high eigenvalue in the Attention domain may imply that attention is a strong common factor, which may overlap or interact with other cognitive functions being assessed. Alternatively, the high eigenvalue may be reflective of common method variance being captured in the first factor.

These domains were included in the 24-item version as they accounted for the most variance in the data, with eigenvalues ≥1. When using this 24-item instrument, both total and individual domain scores are computed.

The test–retest reliability coefficients for the 24-item instrument ranged between 0.49 and 0.74, with coefficients for four of the five domains (attention, executive functioning, communication and bother) falling below 0.70, a value that some have suggested to be the minimum standard for demonstrating reliability [23]. However, a number of factors should be considered when interpreting these coefficients, not least the fact that patients

included in the test–retest reliability analysis were part of an interventional study, albeit they were treated with placebo. Although these patients are more likely than their BI 409306-treated counterparts to respond in a consistent way across visits, it is still possible that patients experienced a placebo or study effect, which may have affected their performance leading to a lack of agreement between responses over the two visits. While this effect would reduce test–retest reliability, it would also indicate the high level of construct validity of the PRECIS and allow for greater sensitivity to between-group differences in treatment studies. Such tradeoffs between reliability and validity are common in clinical research, including in studies of cognitive change in schizophrenia [26]. Nonetheless, the test–retest analysis coefficients were supported by moderate to high levels of agreement across visits (60.4%–74.8%), demonstrating adequate test–retest reliability in the context of the current study.

It is worth noting that the primary outcome in the clinical, pharmacological study from which the patient group was enrolled was to observe a change in cognitive function, as measured by the CANTAB. The purpose of developing the PRECIS instrument was to detect treatment responsiveness by comparing any changes in outcome during treatment with corresponding CANTAB scores. However, as no treatment effect was observed using the validated CANTAB score, treatment responsiveness of the PRECIS instrument could not be assessed. Therefore, the sensitivity of PRECIS to detect differences corresponding with changes in clinical symptom severity requires further exploration. Continued development of the PRECIS instrument is ongoing, including the use of the 35-item version in another Phase II study in CIAS to generate additional data to support the proposed revisions reported here and to obtain treatment responsiveness data. Future work may also involve the inclusion of the PRECIS instrument in a study of cognitive remediation, as a previous study has demonstrated that a moderate effect size for improvement in cognition (0.5 SD), as measured by MCCB, can be achieved using cognitive remediation [27].

While the current study cannot confirm sensitivity of the PRECIS instrument to severity of positive or negative symptoms, the patients eligible for this study comprised a subset of patients with schizophrenia who were taking regular antipsychotic medication (for ≥8 weeks prior to randomization) and with no more than moderate hallucinations, delusions, or depression. While the PRECIS instrument was not developed to measure the severity of positive or negative symptoms, further investigation is needed to fully understand the reliability and validity of the PRECIS instrument in patients with a wide range of symptom severity.

The final stage of the development and validation process was to determine the algorithm to be used to convert the Likert responses into item, domain, and total scores. Further investigation may identify alternatives to the chosen scoring algorithm that may impact on the sensitivity and suitability of the instrument. For example, by increasing or decreasing the influence of the Bother scores relative to that of the other four domain scores, further gains in validity may be observed.

The study has a number of limitations to be considered. First, assessment of reliability and discriminant validity may have been impacted by the differing sizes and characteristics of the patient and control groups, including lower mean age in control subjects and a lower proportion of African American subjects. Furthermore, responses from control subjects demonstrated floor effects with limited range in scores, which may have influenced the assessment of discriminant validity. Second, the patient sample included predominantly African-American subjects, therefore may not be representative of all patient populations. It should also be noted that the performance-based measures MCCB and CANTAB, which were applied a number of times throughout the study, have been shown to have small practice effects, which may have influenced the assessment of convergent

validity. However, this would not have impacted test–retest reliability of the subjective PRECIS instrument. Finally, a CFA utilizing classic structural equation modelling to test the absolute fit of our five-factor PRECIS model was not performed and should be pursued in future research to confirm findings.

Conclusions

In conclusion, a revised 24-item PRECIS instrument has been developed that shows good reliability and validity. This tool may provide a patient-based perspective to complement existing measures of cognition and serves to define key patient-based endpoints for use in future clinical studies.

Abbreviations

CANTAB, Cambridge Automated Neuropsychological Test Battery

CFA, confirmatory factor analysis

CIAS, cognitive impairment associated with schizophrenia

EFA, exploratory factor analysis

EOT, end of treatment

ICCs, intra-class correlation coefficients

IRB, institutional review board

MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia

MCCB, MATRICS Consensus Cognitive Battery

PRECIS, Patient-Reported Experience of Cognitive Impairment in Schizophrenia

PROs, patient-reported outcomes

SASCCS, Self-Assessment Scale of Cognitive Complaints in Schizophrenia

SCoRS, Schizophrenia Cognition Rating Scale

SD, standard deviation

SSTICS, Subjective Scale to Investigate Cognition in Schizophrenia

Declarations

Ethics Approval and Consent to Participate

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, International Council for Good Clinical Practice, and applicable country-specific regulatory requirements. It was reviewed by

the New England Research Institute's institutional review board (IRB) and each study site received individual IRB approval via Alpha IRB. Prior to patient participation, written informed consent was obtained from each patient or the patient's legally accepted representative. Each signature was dated by each signatory and the informed consent and any additional patient information form was retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information was given to each patient or the patient's legally accepted representative.

Consent for Publication

Not applicable

Availability of Data and Material

The datasets generated and/or analysed during the current study are not publicly available as they are currently under regulatory review but may be available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there are no conflicts of interest in relation to the subject of this study. BD is an employee of Synexus and has been the principal investigator on studies for Boehringer Ingelheim but received no direct payments for the development of this manuscript. AS is a consultant of Boehringer Ingelheim and has received research support from J&J PRD, Sunovion, Alkermes, Allergan, Envivo, Lundbeck, Takeda, Neurium, Intracellular, vTv Therapeutics, Avanir, Roche, Otsuka, Alder, and Acadia. DPW receives grant and research support from Novartis, J&J PRD, Sunovion, Janssen, Pfizer, AbbVie, Alkermes, Allergan, Takeda, Otsuka, Zogenix, Omeros, CoMentis, IntraCellular, Lupin, Avanir, Lundbeck, and Roche, and serves as a consultant for Otsuka, Janssen, and Acadia. SS was a paid consultant for Boehringer Ingelheim and New England Research Institutes (NERI) during the process of scale development. DCH received institutional support for the study and receives grant support from NIMH, Otsuka Pharmaceuticals, and Roche Translational and Clinical Research Center, Inc. RCR was an employee of NERI at time of study. NERI was contracted to conduct the study. MG and MS are employees of Boehringer Ingelheim Pharmaceuticals, Inc., which owns the PRECIS instrument, but received no direct compensation related to the development of this manuscript. JJT was an employee of Boehringer Ingelheim Pharmaceuticals, Inc. during the development of the PRECIS instrument and is now an employee of Janssen Global Services. LD has nothing to disclose.

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Authors' Contributions

The authors met the criteria for authorship as recommended by the International Committee of Medical Journal Editors. SS contributed to the conception and design of the PRECIS instrument. RCR, JJT, DCH, MG, LD, and MS contributed to the study concept and design. RCR, AS, and DPW contributed to data acquisition. RCR, MG, and MS contributed to the analysis. RCR, JJT, SS, DCH, AS, DPW, MG, BD, LD, and MS all contributed to the

interpretation of the results, were involved in the preparation and review of the manuscript, approved the final version to be submitted and agree to be accountable for all aspects of the work.

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Tables

Table 1. Demographic characteristics

	Patients with schizophrenia (N=410)*	Controls (N=88)	*p*-value
Gender, n (%)			0.0001
Female	126 (30.7)	47 (53.4)	
Male	284 (69.3)	41 (46.6)	
Ethnicity, n (%)			0.32
Hispanic or Latino	37 (9.0)	11 (12.5)	
Not Hispanic or Latino	373 (91.0)	77 (87.5)	
Race, n (%)			<0.0001
American Indian or Alaska Native	1 (0.24)	0 (0.0)	
Asian	16 (3.90)	7 (8.0)	
Black or African American	243 (59.27)	20 (22.7)	
Multiple	3 (0.73)	0 (0.0)	
Native Hawaiian or other Pacific Islander	1 (0.24)	0 (0.0)	
White	146 (35.61)	61 (69.3)	
Age, years			
Mean (SD)	43.0 (9.5)	33.2 (11.1)	<0.0001
Median (Q1, Q3)	45 (36, 51)	29 (24, 42)	

*Number of subjects with PRECIS data at Visit 2 (randomization). PRECIS, Patient-Reported Experience of Cognitive Impairment of Schizophrenia; SD, standard deviation; Q1, first quartile; Q3, third quartile.

Table 2. Factor loadings*, eigenvalues and proportion of variance for the revised PRECIS scale (22-item† preliminary CFA)

	Factor pattern			
Item code and wording as it appears in the PRECIS instrument	Memory (Factor 2)	Attention (Factor 1)	Executive Function (Factor 3)	Communication (Factor 4)
CIAS103 - Remembering where I put things (for example, my keys, phone, glasses, or other items) was...	**0.72622**	0.18842	0.22142	0.08464
CIAS101 - Recalling people’s names was...	**0.69699**	0.22717	0.17628	0.12388
CIAS102 - Remembering what I was supposed to do or buy was...	**0.68651**	0.28317	0.26065	0.13626
CIAS105 - Recalling something from a couple of years ago when I wanted to (for example, information I used to know or an important event) was...	**0.67776**	0.12408	0.20716	0.10645
CIAS104 - When I wanted to remember information from a short time ago (for example, what I read or watched in a movie or TV show), it was...	**0.66697**	0.32181	0.14880	0.22711
CIAS107 - Remembering what someone else was saying was...	**0.61461**	0.09241	0.16753	0.46971
CIAS106 - Remembering what I wanted to say was...	**0.55942**	0.25941	0.12588	0.44045
CIAS129 - My thoughts were racing and speeding through my mind faster than I wanted.	0.09744	**0.71819**	0.35912	0.11131
CIAS133 - I felt like my thoughts were blocked and nothing was coming to my mind.	0.30631	**0.70485**	0.00639	0.20316
CIAS130 - My thinking was unclear, cloudy, or foggy.	0.22416	**0.68480**	0.26346	0.27119
CIAS128 - I kept thinking about things even when I wanted to let them go.	0.18538	**0.68465**	0.42184	0.05263
CIAS131 - I felt like my thinking was not as fast as other	0.28484	**0.66222**	0.16964	0.25322

people's.				
CIAS125 - My mind drifted off when I wanted to pay attention.	0.30588	**0.63926**	0.21644	0.20564
CIAS121 - When someone I know changed our plans at the last minute, it was...	0.20847	0.20540	**0.72452**	-0.00210
CIAS120 - When things don't happen the way they usually do, it was...	0.20219	0.23072	**0.71328**	0.14101
CIAS124 - Understanding how something happening now will affect me in the future was...	0.20254	0.25629	**0.65102**	0.22837
CIAS123 - Figuring out a new way to get something done was...	0.21123	0.25480	**0.62250**	0.30620
CIAS122 - Coming up with solutions to problems was...	0.28439	0.25127	**0.58911**	0.29553
CIAS115 - Understanding body language, gestures, or other hints from people without them telling me how they felt in words was...	0.13941	0.01946	**0.57743**	0.401 40
CIAS113 - Explaining myself well so that other people knew what I meant was...	0.15158	0.19430	0.32746	**0.75310**
CIAS114 - Finding words to say what I mean was...	0.28991	0.27175	0.27366	**0.72602**
CIAS111 - Coming up with something to say when I wanted to was...	0.19762	0.29561	0.14496	**0.68641**

Eigenvalue	1.51987123	9.73519200	1.32470800	1.09902980
Difference	0.19516323	8.21532078	0.22567820	0.21401339
Proportion	0.0691	0.4425	0.0602	0.0500
Cumulative	0.5116	0.4425	0.5718	0.6218

*Factor loadings from Varimax rotation of baseline data in NCT02281773; †CIAS questions #134 and 135 were excluded from the confirmatory factor analysis for conceptual reasons. These two items make up the fifth factor, 'Patient Bother' and fall within Factor 1 (Attention).. Numbers in bold denote the factor to which each item was predominantly loaded. PRECIS 24-item instrument provided in Additional Table A4.

CFA, confirmatory factor analysis; CIAS, cognitive impairment associated with schizophrenia; PRECIS, Patient-Reported Experience of Cognitive Impairment of Schizophrenia.

Table 3. Internal reliability of the PRECIS instrument (24-item version)

		Internal consistency (n=410)				Test–retest (n=111)†		
	PRECIS item	Cronbach's alpha	Cronbach's alpha with item removed§	Correlation with total¶	Inflation (%)‡	ICC	% agreement**	*p*-value††
	Total scale	**0.942**				**0.78**	**73.0**	**0.89**
Domain 1 (Attention)	**Overall**	**0.873**				**0.65**	**60.4**	**0.57**
	CIAS125		0.853	0.67	-2.32			
	CIAS128		0.846	0.70	-3.05			
	CIAS129		0.849	0.69	-2.76			
	CIAS130		0.846	0.71	-3.04			
	CIAS131		0.854	0.66	-2.17			
	CIAS133		0.859	0.63	-1.57			
Domain 2 (Memory)	**Overall**	**0.873**				**0.74**	**74.8**	**0.79**
	CIAS101		0.857	0.64	-1.89			
	CIAS102		0.850	0.70	-2.64			
	CIAS103		0.854	0.66	-2.22			
	CIAS104		0.849	0.69	-2.72			
	CIAS105		0.866	0.59	-0.85			
	CIAS106		0.856	0.65	-1.98			
	CIAS107		0.854	0.66	-2.20			
Domain 3 (Executive function)	**Overall**	**0.845**				**0.62**	**67.6**	**0.80**
	CIAS115		0.841	0.52	-0.49			
	CIAS120		0.815	0.65	-3.62			
	CIAS121		0.825	0.60	-2.36			
	CIAS122		0.813	0.66	-3.82			
	CIAS123		0.810	0.68	-4.13			
	CIAS124		0.814	0.66	-3.74			
Domain 4 (Communication)	**Overall**	**0.824**				**0.49**	**62.2**	**0.93**
	CIAS111		0.833	0.60	1.07			
	CIAS113		0.723	0.71	-12.23			
	CIAS114		0.701	0.73	-14.91			
Domain 5	**Overall**	**0.743**				**0.64**	**60.4**	**0.53**

(Bother)	CIAS134	*	0.60	*
	CIAS135	*	0.60	*

ot able to be estimated due to insufficient number of domain items; †item-level ICC and percentage agreement analyses were conducted to avoid duplicating total and domain analyses; §Cronbach alpha after removing the item from the scale; earson correlation between an individual item and the sum of the remaining items that constitute the scale; ‡percent inflation Cronbach alpha after removing item from the scale; **item scores at Visit 5 and EOT were rounded to nearest integer prior to nputing % agreement; ††*p*-value for test of difference between mean scores at Visit 5 and EOT.

AS, cognitive impairment associated with schizophrenia; EOT, end of treatment; ICC, intra-class correlation; PRECIS, ient-Reported Subjective Experience of Cognitive Impairment of Schizophrenia.

Table 4. Discriminant validity of the revised 24-item PRECIS domain scores

	Patients with schizophrenia (N=410)	Controls (N=88)		
Domain	**Mean (SD)**	**Mean (SD)**	**Mean difference (SD)**	**Unadjusted *p*-value**
Revised PRECIS scale (24 items)	2.10 (0.76)	1.42 (0.37)	-0.69 (0.70)	<0.0001
Domain 1 (Attention)	2.29 (0.99)	1.50 (0.49)	-0.79 (0.92)	<0.0001
Domain 2 (Memory)	2.02 (0.83)	1.45 (0.42)	-0.58 (0.77)	<0.0001
Domain 3 (Executive Function)	2.06 (0.85)	1.37 (0.42)	-0.69 (0.80)	<0.0001
Domain 4 (Communication)	1.84 (0.86)	1.30 (0.47)	-0.54 (0.81)	<0.0001
Domain 5 (Bother)	2.35 (1.16)	1.41 (0.65)	-0.94 (1.09)	<0.0001

PRECIS, Patients-Reported Experience of Cognitive Impairment of Schizophrenia; SD, standard deviation.

Table 5. Convergent/divergent validity* of SCoRS, MCCB, and CANTAB scores and 24-item PRECIS domain/total scores (N=379)

	Domain 1 (Attention)	Domain 2 (Memory)	Domain 3 (Executive Function)	Domain 4 (Communication)	Domain 5 (Bother)	Total scale
Global	0.38 (**<0.0001**)	0.39 (**<0.0001**)	0.35 (**<0.0001**)	0.33 (**<0.0001**)	0.32 (**<0.0001**)	0.43 (**<0.0001**)
composite	-0.055 (0.29)	-0.086 (0.10)	-0.110 (**0.03**)	-0.043 (0.40)	0.027 (0.60)	-0.086 (0.09)
d ocessing	-0.049 (0.34)	-0.039 (0.45)	-0.091 (0.08)	-0.011 (0.84)	0.002 (0.97)	-0.068 (0.18)
tion/vigilance	-0.077 (0.13)	-0.112 (**0.03**)	-0.099 (**0.05**)	-0.032 (0.54)	-0.044 (0.40)	-0.104 (**0.04**)
ing memory	-0.096 (0.06)	-0.138 (**0.01**)	-0.129 (**0.01**)	-0.047 (0.36)	0.014 (0.78)	-0.118 (**0.02**)
al learning	-0.092 (0.07)	-0.067 (0.19)	-0.060 (0.24)	-0.075 (0.15)	0.045 (0.38)	-0.074 (0.15)
l learning	-0.020 (0.69)	-0.027 (0.59)	-0.058 (0.26)	-0.042 (0.42)	0.073 (0.16)	-0.043 (0.40)
oning and em solving	-0.010 (0.85)	0.009 (0.86)	-0.087 (0.09)	-0.002 (0.97)	0.005 (0.93)	-0.030 (0.56)
l cognition	0.067 (0.19)	-0.050 (0.33)	-0.021 (0.68)	-0.017 (0.75)	0.089 (0.08)	0.006 (0.90)
AB composite	-0.052 (0.31)	-0.041 (0.43)	-0.082 (0.11)	0.023 (0.66)	-0.001 (0.99)	-0.055 (0.29)
ion time: d of ssing	-0.040 (0.44)	-0.014 (0.78)	0.026 (0.62)	-0.095 (0.06)	0.021 (0.68)	-0.013 (0.80)
al /Recognition ory: al learning	-0.070 (0.17)	-0.105 (**0.04**)	-0.040 (0.44)	-0.043 (0.40)	-0.040 (0.44)	-0.071 (0.17)
al working ory: Working ory	0.050 (0.34)	-0.035 (0.50)	0.044 (0.39)	-0.034 (0.51)	-0.041 (0.43)	0.009 (0.86)
l visual	-0.018	-0.016	-0.047	0.020 (0.70)	-0.021	-0.026 (0.61)

nation ssing: tion/vigilance	(0.73)	(0.76)	(0.36)		(0.68)	
d associates ing: Visual ing	0.055 (0.28)	0.039 (0.45)	0.057 (0.27)	-0.025 (0.63)	0.014 (0.79)	0.050 (0.33)
ion nition task: l cognition	-0.030 (0.56)	-0.033 (0.53)	-0.078 (0.13)	-0.016 (0.76)	0.044 (0.39)	-0.046 (0.37)
Touch ings of ridge: oning and em solving	-0.042 (0.42)	-0.060 (0.25)	-0.073 (0.16)	-0.028 (0.59)	0.038 (0.47)	-0.056 (0.28)
tion hing task: oning and em solving	0.031 (0.55)	0.055 (0.29)	0.014 (0.78)	0.003 (0.95)	0.067 (0.19)	0.039 (0.45)

s are Spearman correlations (*p*-values). Statistically significant *p*-values (≤0.05) in bold.

B, Cambridge Automated Neuropsychological Test Battery; MCCB, Measurement and Treatment Research to Improve on in Schizophrenia (MATRICS) Consensus Cognitive Battery;

S, Patients-Reported Experience of Cognitive Impairment of Schizophrenia; SCoRS, Schizophrenia Cognition Rating Scale.

Additional File

Additional File 1.docx includes the analysis of the 35-item PRECIS Instrument, including the initial exploratory factor analysis and the results of reliability and validity assessments. The 35-item, five-domain, draft PRO instrument for CIAS is provided in addition to an item elimination summary, the revised 24-item PRECIS scale, and the results for the 22-item preliminary CFA.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRECISmsCONSORTChecklistJuly162019.doc

- PRECISAdditionalFIle1.pdf