Exploring the "Insight Paradox" in Treatment-Resistant Schizophrenia: Correlations Between Dimensions of Insight and Depressive Symptoms in Patients Receiving Clozapine

ABSTRACT

Objective: There remains a lack of clarity as to the possible cross talk of insight into illness and depressive symptoms in treatment-resistant schizophrenia. We therefore set our primary aim to evaluate relationship between insight dimensions and depressive symptoms in patients with treatment-resistant schizophrenia receiving clozapine.

Methods: This was a cross-sectional, non-interventional study, conducted in daily clinical practice conditions. Patients in outpatient clinics between March 2020 and May 2020 with treatment-resistant schizophrenia (based on Treatment Response and Resistance in Psychosis), with no comorbid psychiatric disorder, and with no body mass index greater than 40.0 kg/m^2 were included. We collected sociodemographic variables, scores of insight dimensions (treatment compliance, illness recognition, and symptom relabeling with the Schedule for Assessment of Insight), and depressive symptoms with Calgary Depression Score for Schizophrenia. Linear regression models were used to investigate variables associated with depressive symptoms as the outcome of interest.

Results: The final analysis sample comprised 55 patients with treatment-resistant schizophrenia, with a mean age of 42.48 (SD = 9.18) years and a predominance of the male sex (n = 42, 76.9%). Model 1 [Calgary Depression Score for Schizophrenia ~ (Schedule for Assessment of Insight + Positive and Negative Syndrome Scale)] displayed that 48% of the variation in the Calgary Depression Score for Schizophrenia can be explained by Schedule for Assessment of Insight—composite and Positive and Negative Syndrome Scale—composite (P < .001). More effectively, model 2 [Calgary Depression Score for Schizophrenia ~ (Schedule for Assessment of Insight—illness recognition + Positive and Negative Syndrome Scale—general psychopathology)] revealed that 51% of the variation in the Calgary Depression Score for Schizophrenia can be explained by the sub-scales (P < .001). We further designed a new model in which Global Assessment of Functioning scores were the response variable to explore the link between awareness into illness and functionality (Global Assessment of Functioning ~ Schedule for Assessment of Insight—illness recognition). In this model, awareness of illness did not explain a significant proportion of variance in functionality scores ($R^2 = 0.045$, $F(1,52) = 2.48$, $P = 0.121$).

Conclusion: The treatment compliance part of insight was not one of the significant explanatory variables of depressive symptoms, but it explained the variance in functioning, in contrast to the illness recognition dimension of insight. If our findings were replicated in treatment-resistant schizophrenia, they would suggest that promoting treatment compliance dimension of insight instead of recognition of illness could not increase depressive symptoms.

Keywords: Schizophrenia, treatment-resistant schizophrenia, insight, depressive symptoms, functionality

Süleyman Dönmezler[1] [ID]
Gizem İskender[2] [ID]
Nurhan Fıstıkcı[3] [ID]
Yavuz Altunkaynak[4] [ID]
Sevinç Ulusoy[5] [ID]
Tonguç Demir Berkol[5] [ID]

[1]Department of Psychiatry, Başakşehir Çam and Sakura City Hospital, Istanbul, Turkey
[2]Department of Psychiatry, Prof. Dr. Cemil Taşcıoğlu City Hospital, Istanbul, Turkey
[3]Department of Social Sciences, Gelişim University, Istanbul, Turkey
[4]Department of Neurology, Başakşehir Çam and Sakura City Hospital, Istanbul, Turkey
[5]Department of Psychiatry, Neurology and Neurosurgery, Bakırköy Training and Research Hospital for Psychiatry, Istanbul, Turkey

Corresponding author:
Süleyman Dönmezler
✉ suleymandonmezler@icloud.com

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Alpha Psychiatry 2023;24(3):102-107

Introduction

Insight into disorder is a term that encompasses awareness of a psychiatric disorder, awareness of the need for treatment, recognition of distinct signs and symptoms of the disorder, and the relabeling of the symptoms of the disorder and understanding of the social ramifications of the disorder.[1] Considering that psychosis is characterized by impairment in the ability to assess reality, we often encounter lack of insight in schizophrenia, though not always. Partially or totally lacking of insight has been shown in 50%-80% of individuals diagnosed with schizophrenia.[2,3]

Over the past 30 years, studies that inquire insight and psychopathology association have gained traction.[4,5] The assessment of insight has evolved from traditional dichotomous (all-or-none) to multidimensional approach throughout these years. Awareness of having an illness, awareness of a need for treatment, and awareness of the consequences of the disorder are 3 aspects of appraisal of the insight into psychosis.[6] Besides the emergence and evolution of multidimensional assessment, insight can also be evaluated dynamically. For example, fluctuation in insight rather than baseline measuring the insight may predict suicidal behavior in psychosis.[7]

Mounting findings have revealed correlations of insight between clinical aspects of psychosis. Insight into illness has been consistently linked to better treatment adherence in psychosis.[8-10] Likewise, impaired insight is clinically prominent and predicts poor medication adherence,[11] relapse and readmission,[12] and reduced functionality.[13] Poor clinical insight further leads to delay in access to treatment and weakens maintenance of it.[14] However, higher insight is not always linked with positive outcomes. Greater awareness of illness was associated with hopelessness,[15] is a predictor of suicidality,[16-18] and has been linked to depression.[19]

About 20%-30% of patients diagnosed with schizophrenia show treatment-resistant features[20,21] presented at the onset of disorder or over time[22,23] Despite severe adverse effects such as reduced gastrointestinal mobility, cardiomyopathy, and agranulocytosis, clozapine is the best treatment option in treatment-resistant schizophrenia (TRS).[24] Clozapine improves insight into illness in patients with schizophrenia after 6 months on the treatment.[25]

MAIN POINTS

- There remains a lack of clarity as to the possible cross talk of insight into illness and depressive symptoms in treatment-resistant schizophrenia (TRS).
- The assessment of insight has evolved from traditional dichotomous (all-or-none) to multidimensional approach.
- The Schedule for Assessment of Insight (SAI) was used to assess insight and its dimensions: (i) treatment compliance, (ii) awareness of mental illness, and (iii) relabeling of psychotic symptoms as abnormal.
- In our model, the dimension of insight related to the (ii) recognition of mental illness explained depressive symptoms, but it did not contribute the variability of functioning in the context of the TRS.
- The treatment compliance dimension of insight was not associated with depressive symptoms in contrast to the illness recognition dimension.

Despite foregoing correlations being established, there remains a lack of clarity as to the possible cross talk of insight into illness and depressive symptoms in TRS. We therefore set our primary aim to evaluate relationship between insight dimensions and depressive symptoms in patients with TRS receiving clozapine. Second, we aimed to evaluate the correlations between the insight and clinical characteristics of the participants. Our double-sided hypothesis was "There is an association between insight into illness and depressive symptoms of TRS patients receiving clozapine."

Methods

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and approval for the study was granted by the Specialism in Medicine Commission of University of Health Sciences, Bakirkoy Prof Dr Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery with protocol number 245 on December 7, 2018. All participants provided written informed consent after the study procedures were fully explained. This study was reported according to the guidelines for cross-sectional studies in the Strengthening the Reporting of Observational Studies in Epidemiology checklist.

Study Design and Settings

We conducted a cross-sectional study in which all patients diagnosed with treatment-resistant schizophrenia receiving clozapine for at least 6 months in University of Health Sciences, Bakirkoy Prof Dr Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery outpatient clinics between March 2020 and May 2020 were included.

Patients

In the period between the aforementioned dates, we included all adult outpatients who presented to outpatient clinics with signs and symptoms covering all DSM-5 (Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition) schizophrenia diagnostic criteria[26] and who were diagnosed by a psychiatrist. We did not include participants who were clinically suspected of schizophrenia (e.g., those with a diagnosis of unspecified psychosis not due to a substance or known physiological condition) or who were diagnosed with comorbid psychiatric disorders (such as major depression). We had planned to exclude patients with substance use disorder. Additionally, having a body mass index greater than 40.0 kg/m^2 was the other exclusion criterion.

Treatment-Resistant Schizophrenia

Based on Treatment Response and Resistance in Psychosis working group consensus, TRS was diagnosed based on the following criteria: (i) the duration of the symptoms $\geq$12 weeks and a decrease of <20% in the Positive and Negative Symptom Scale (PANSS) after 6 weeks of treatment/observation, (ii) $\geq$2 different antipsychotics for $\geq$ 6 weeks and $\geq$600 mg/g chlorpromazine equivalent dose, and (iii) confirmation of the use of $\geq$80% of the prescribed doses in the previous treatment, with the follow-up of the drug and medical records, by patient/carer reporting.[27]

Data Collection

Medical records, nursing records, consulting notes, and laboratory tests were collected and reviewed by trained medical investigators. The medical investigators interviewed the patients after

determining TRS based on a retrospective analysis of the medical records. Functioning of the participants was assessed with the Global Assessment of Functioning (GAF).[28]

Depressive Symptoms

We assessed depressive symptoms with Calgary Depression Score for Schizophrenia (CDSS). Calgary Depression Score for Schizophrenia was specifically developed to evaluate depressive symptoms in patients diagnosed with schizophrenia. The Calgary Depression Score for Schizophrenia is a 9-item structured interview scale that is reliable in Turkish[29] and valid without overlap with extrapyramidal or negative symptoms.[30] Reliability analysis of CDSS of our sample rendered a Cronbach's $\alpha = 0.854$.

Insight Dimensions

The Schedule for Assessment of Insight (SAI) was used to assess insight and its dimensions. The SAI is a semi-structured interview that provides separate and composite insight scores based on David's model: (i) treatment compliance, (ii) awareness of mental illness, and (iii) relabeling of psychotic symptoms as abnormal.[4] Scale analysis of our data revealed Cronbach's $\alpha = 0.551$.

Independent Variables

We collected data on demographics [age, sex, education, and work status (in work and outside working force)] and clinical characteristics (number of hospitalization, duration of clozapine treatment, and current clozapine dose). Likewise, we gathered scores of the Turkish version[31] of the PANSS[32] scores ["general psychopathology," "negative symptoms," "positive symptoms," and composite (in this study, Cronbach's $\alpha = 0.854$)] and SAI ("treatment compliance," "illness recognition," "symptom relabeling," and composite).

Statistical Methods

Continuous variables are presented as mean (SD) and median with 25th and 75th percentiles of the distribution, and categorical variables are described as frequency and percentage.

In our primary analyses, simple linear regression models were used to investigate variables associated with depressive symptoms as the outcome of interest. Explanatory variables were entered into the model based on past researches and hierarchical regression method. Known explanatory variables have been entered after which possible independent variables of the outcome were included in the linear model. To compare the fit of the models, we compared R^2 and AIC (Akaike Information Criterion) values of them. AIC (less is good) was also used to penalize the model having additional variables which might entail higher R^2 values.[33] Besides, standardized estimates can be used to directly compare magnitudes of explanatory variables.

An $\alpha = 5\%$ was accepted as the statistical significance of any results. All the analyses and visualizations were performed using "The R Base," "glm2," and "AICcmodavg" package of the R software version 3.6.0(R Foundation for Statistical Computing, Austria, 2019).[34]

Results

Six hundred forty-three patients with schizophrenia were considered for analyses; however, 418 patients without TRS and 168 patients that administered non-clozapine medication were excluded. Of 57 patients with a preliminary diagnosis of TRS, we excluded 2 of them because of the comorbidity of morbid obesity (Figure 1).

We included 55 patients with TRS, with a mean age of 42.48 (SD = 9.18 years and a predominance of the male sex (n = 42, 76.9%). Detailed descriptive analyses are reported in Table 1.

Prior to measuring adjusted estimates, each variable given in Table 1 was examined in simple linear regression models, in which CDSS was the outcome variable (Supplementary Table 1).

In the first model (model 1), composite scale scores were entered ($R^2 = 0.480$, AIC = 302, $P < .001$). In the second model (model 2), subscales that produce more weight than other variables in primary analyses were entered ($R^2 = 0.510$, AIC = 299, $P < .001$). Model 1 [CDSS ~ (SAI + PANSS)] displayed that 48% of the variation in the CDSS can be explained by SAI—composite and PANSS—composite. More effectively, model 2 [CDSS ~ (SAI—illness recognition + PANSS—general psychopathology)] revealed that 51% of the variation in the CDSS can be explained by the sub-scale shown in Table 2.
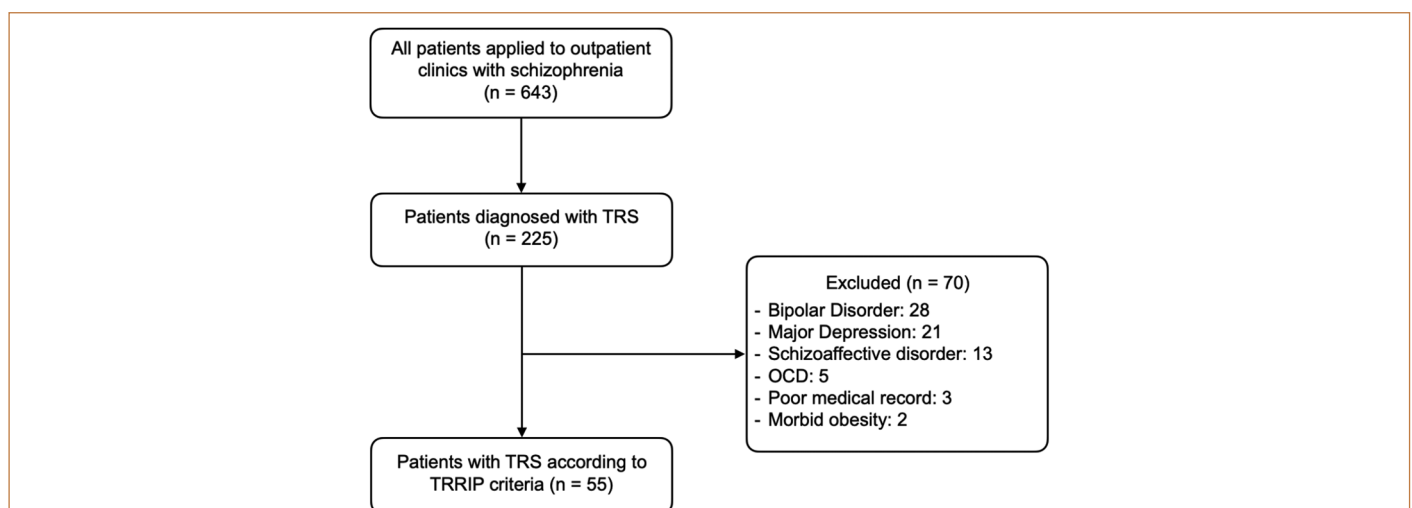

Figure 1. Flow diagram of the patients considered for and included in final analyses. n, sample size; OCD, obsessive compulsive disorder; TRRIP, Treatment Response and Resistance in Psychosis; TRS, treatment-resistant schizophrenia.

Table 1. Characteristics of TRS Patients Receiving Clozapine

Variable	All Participants n = 54
Age, years	42.48 (SD = 9.18)
Female, n (%)	13 (SD = 24.1)
Highest education achieved, years	9.91 (SD = 3.33)
Work status, in work, n (%)	10 (SD = 18.5)
Has spouse/partner, n (%)	10 (SD = 18.5)
Clozapine dose, mg/day	350.0 (200.0-487.5)
Duration of clozapine treatment, years	10.0 (4.0-15.0)
Number of hospitalizations	4.57 (SD = 4.47)
PANSS—positive symptoms	15.0 (SD = 5.97)
PANSS—negative symptoms	23.6 (SD = 6.87)
PANSS—general psychopathology	37.6 (SD = 10.2)
PANSS—composite	76.1 (SD = 18.9)
SAI—treatment compliance	3.37 (SD = 1.17)
SAI—illness recognition	3.30 (SD = 2.43)
SAI—symptom relabeling	2.04 (SD = 1.34)
SAI—composite	8.70 (SD = 3.77)
CDSS	4.97 (SD = 5.17)
GAF	50.6 (SD = 14.6)

Data are presented as mean (SD) or median (25th percentile-75th percentile) for continuous variables and frequency (percentage) for categorical variables.
CDSS, Calgary Depression Score for Schizophrenia; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale; SAI, Schedule for Assessment of Insight; TRS, treatment-resistant schizophrenia.

We further designed a new model in which GAF scores were the response variable to explore the link between awareness into illness and functionality (GAF ~ SAI—illness recognition). In this model, awareness of illness did not explain a significant proportion of variance in functionality scores ($R^2 = 0.045$, $F(1,52) = 2.48$, $P = 0.121$).

As one of our secondary aims, we investigated the relationship between age and insight. The "age" and "SAI—composite" scatterplot and the "age" and "SAI—treatment compliance" scatterplots illustrated curvilinear second-order polynomial trend lines (Supplementary Figure 1).

Discussion

Herein, we describe the significant association between insight and depressive symptoms in patients with TRS receiving clozapine. While treatment compliance and the relabelling of psychotic symptoms as

insight sub-scales fail to account for variability in depressive symptoms, the model that assigns a high weight to the awareness of illness sub-scale significantly explains the proportion of variance in participants' depression scores. Furthermore, we did not find a relationship between awareness of illness and functionality.

The findings of this paper should be considered in the light of limitations posed by the cross-sectional design of the study. Our study had some limitations. Missing data of other possible confounders such as internal stigmatization, social cognition, and metacognition of the patients are significant of these. Neurophysiological monitoring and imaging modalities that could contribute objective findings related to insight into illness were not performed. Finally, the study sample was obtained at a single center, and so the conclusions may not be generalized to other institutions.

Impaired insight into illness, which is a prevailing feature of schizophrenia,[35-37] impacts treatment adherence. Lack of adherence to treatment in patients with schizophrenia, in turn, exerts as one of the major risk factors for relapse,[38] rehospitalization,[39] and violent behavior of patients.[40] Impaired insight is also associated with greater positive symptoms.[41,42] A modest relationship between negative symptoms and poor insight was observed.[43] Patients exhibiting diminished insight tend to experience a reduced quality of life, inferior social relationships, and less favorable occupational outcomes[44-46]. Although foregoing correlations between impaired insight and poor outcomes appear undesirable, improvement in insight in patients with schizophrenia may worsen mood, as the "insight paradox" posits. In addition, awareness of illness may be necessary but is not a quintessential factor of treatment adherence.[10] Impaired insight would protect against depressive symptoms in the early stages of schizophrenia.[47] Moreover, the internal stigmatization of mental illness may transform into the recognition of painful event, and, in turn, depression risk could increase.[48] Trends in the movement of renaming schizophrenia in Asia to reduce the stigma among patients with schizophrenia[49] may imply the awareness of illness, and naming it would not necessarily be a contributor to positive outcome in mental health care.

In our study, the illness recognition dimension of insight explained depressive symptoms but did not contribute to functioning in TRS. Conversely, the treatment compliance part of insight was not one of the significant explanatory variables of depressive symptoms, but it explained the variance in functioning. Overall, the treatment compliance dimension of insight was not associated with

Table 2. Comparison of 2 Hierarchical Linear Regression Models in which CDSS was Designed as the Response Variable (n = 54)

Variable	Estimate	SE	Standardized Estimate	95% CI Lower	95% CI Upper	P
			Model 1			
Intercept	−16.48	3.25				**<.001**
SAI—composite	0.950	0.15	0.694	0.466	0.922	**<.001**
PANSS—composite	0.173	0.03	0.634	0.406	0.862	**<.001**
			Model 2			
Intercept	−8.194	2.11				**<.001**
SAI—illness recognition	1.223	0.21	0.575	0.378	0.773	**<.001**
PANSS—general psychopathology	0.243	0.05	0.478	0.280	0.675	**<.001**

P-values considered statistically significant are denoted in bold.
CDSS, Calgary Depression Score for Schizophrenia; PANSS, Positive and Negative Syndrome Scale; SAI, Schedule for Assessment of Insight.

depressive symptoms in contrast to the illness recognition dimension. Consequently, clinicians may consider incorporating these findings when evaluating and enhancing insight and its associated dimensions in patients with TRS. Additionally, they would consider that recognition of illness may advance depressive symptoms in this patient sub-group. From the perspective of gaining insight into the disorder and enhancing the ability to adhere to treatment as an ultimate clinical goal,[50] the treatment compliance component of insight may prove beneficial for positive outcomes, given its absence of association with depressive symptoms. If our findings are replicated in TRS, they would suggest that promoting treatment compliance dimension of insight instead of recognition of illness could not increase depressive symptoms.

In terms of secondary analysis, in our findings, age was not a confounding factor of the generalized linear model of insight into illness and depressive symptoms. Little is known about the course of the insight over life span. Although further investigations are required, current studies suggest that the impairment of insight follows a U-shaped curvilinear trajectory, in which low level is seen in early and late life and high level is seen over midlife.[51] However, we saw a curvilinear trend in which awareness of illness at the lowest level in early adult improves over midlife and decreases again in late life in our results. To elucidate the impact of aging on insight into illness in schizophrenia, we advocate for a longitudinal study that traces awareness of illness from the onset of the disorder to late life in patients with schizophrenia.

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Supplementary Table 1. Simple Linear Regression Models of Explanatory Variables of the CDSS

Variable	b	95% CI		R^2	Overall Model Test	
		Lower	Upper		F	P
Age	0.00122	-0.155	11.97	0.00000469	0.000244	0.988
Highest education achieved	-0.0067	-0.498	0.364	0.00185	0.0965	0.757
Clozapine dose	0.00751	-8.61E-04	0.016	0.0587	3.24	0.078
Duration of clozapine treatment	-0.0967	-0.272	0.079	0.023	1.22	0.274
PANNS - Positive symptoms	0.154	-0.0829	0.391	0.0317	1.7	0.198
PANSS - Negative symptoms	0.00634	-0.145	0.272	0.00711	0.373	0.544
PANNS- General psychopathology	**0.217**	**0.0889**	**0.345**	0.182	11.6	0.001
PANNS - Composite	**0.0861**	**0.0141**	**0.158**	0.0997	5.76	0.02
SAI - Treatment compliance	-0.329	-1.55	0.896	-0.329	-0.329	0.329
SAI - Illness recognition	**1.13**	**0.633**	**1.63**	0.284	20.6	<.001
SAI - Symptom relabelling	0.862	-0.158	1.88	0.0524	2.88	0.096
SAI - Composite	**0.552**	**0.204**	**0.901**	0.163	10.1	0.002

CDSS: Calgary depression score for schizophrenia, b: Estimate, CI: Confidence interval, PANSS: Positive and negative syndrome scale, SAI: Schedule for assessment of insight, CDSS: Calgary depression score for schizophrenia, GAF: Global assessment of functioning.
Estimates of models in which P values considered statistically significant are denoted in bold.
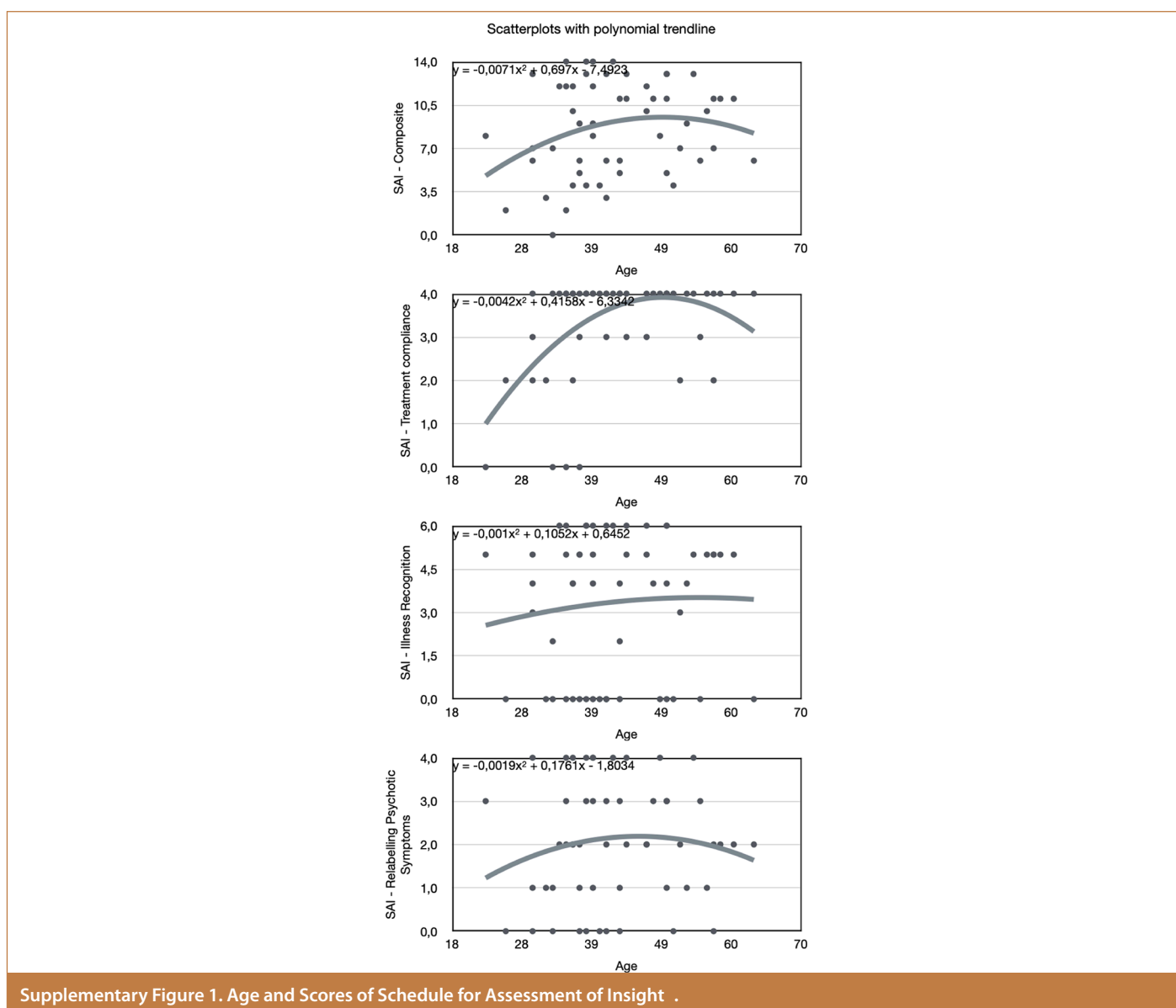
Supplementary Figure 1. Age and Scores of Schedule for Assessment of Insight .