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Relapse Risk Assessment for Schizophrenia Patients (RASP): A New Self-Report Screening Tool

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Abstract

Objectives: The Relapse Assessment for Schizophrenia Patients (RASP) was developed as a six-question self-report screener that measures indicators of Increased Anxiety and Social Isolation to assess patient stability and predict imminent relapse. This paper describes the development and psychometric characteristics of the RASP. **Methods:** The RASP and Positive and Negative Syndrome Scale (PANSS) were administered to patients with schizophrenia (n=166) three separate times. Chart data were collected on a subsample of patients (n=81). Psychometric analyses of RASP included tests of reliability, construct validity, and concurrent validity of items. Factors from RASP were correlated with subscales from PANSS (sensitivity to change and criterion validity [agreement between RASP and evidence of relapse]). **Results:** Test-retest reliability returned modest to strong agreement at the item level and strong agreement at the questionnaire level. RASP showed good item response curves and internal consistency for the total instrument and within each of the two subscales (Increased Anxiety and Social Isolation). RASP Total Score and subscales showed good concurrent validity when correlated with PANSS Total Score, Positive, Excitement, and Anxiety subscales. RASP correctly predicted relapse in 67% of cases, with good specificity and negative predictive power and acceptable positive predictive power and sensitivity. **Conclusions:** The reliability and validity data presented support the use of RASP in settings where addition of a brief self-report assessment of relapse risk among patients with schizophrenia may be of benefit. Ease of use and scoring, and the ability to administer without clinical supervision allows for routine administration and assessment of relapse risk.

Key Words: Schizophrenia, Relapse Assessment, Relapse Risk, Self-Report, Psychometrics

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Introduction

Relapse, or exacerbation of psychotic symptoms, is a frequent driver of hospitalization in schizophrenia (1). Additionally, the clinical deterioration associated with each subsequent relapse increases the burden on the individual, their family, society, and the healthcare system (2). Therefore, one goal of outpatient psychiatric treatment of schizophrenia is control of psychotic symptoms to avoid relapse and hospitalization. Several drivers of relapse have been identified, including prior psychiatric hospitalization (3, 4), antipsychotic medication nonadherence, onset of psychotic symptoms and, to a lesser extent, the presence of active substance abuse (5-

Clinical Implications

The Relapse Risk Assessment for Schizophrenia Patients (RASP) is a self-report tool for assessing risk of relapse for patients with schizophrenia. The reliability and validity data presented here, including RASP's relationship to PANSS scores and relapse over the study period, support the use of this instrument in settings where a brief self-report assessment of relapse risk among patients with schizophrenia may be of benefit. Because the RASP is a patient self-report screener with minimal patient burden and low item difficulty, it requires no training to administer and monitor. The brevity of the form, ease of scoring, and the ability to administer with little or no supervision allows for routine administration and assessment of relapse risk.

Table 1A Relapse Assessment for Schizophrenia Patients: k=6 Items

Item Number	Item Language	Final Disposition*
1	I've been feeling more worried or nervous than usual.	R
2	I've been feeling more restless or tense than usual.	R
3	I've been feeling more angry or irritable than usual.	R
4	I've been staying away from others more than usual.	R
5	I've been getting too little sleep.	R
6	Something specific happened recently that really upset me.	R

*Endorsement of any 3 of the 6 items elevates the patient from low to moderate/high risk of relapse. R=retained after item reduction.

8). However, accurate prediction of relapse remains a challenge for clinicians and other stakeholders (9-12) and may require patient self-report.

The ability to accurately predict relapse in patients with schizophrenia may facilitate more effective matching of therapeutic approach to patient need before relapse, potentially avoiding costly hospitalizations and further decrement of functioning. Though multiple instruments designed to assess psychiatric disease severity have been used to track the likelihood of relapse among psychiatric patients (13, 14), there is a dearth of self-report instruments specifically designed to assess the same among patients with schizophrenia (15). Although there are concerns about the ability of patients with schizophrenia to reliably report on their own symptoms, thoughts, emotions, and behaviors (16-18), self-report questionnaires have successfully been used to assess quality of life, treatment benefits, and medication adherence (19-22). However, there are few tools designed to measure psychiatric symptoms and relapse risk. For example, available patient-reported outcomes (PRO) tools for use in psychiatry may not be specific to schizophrenia relapse (23, 24). Furthermore, the few tools available tend to focus on a single driver, such as attitudes toward medication (25), and many (e.g., Likert scale, free response, dichotomous response) may place an unnecessarily high burden on patients because of their length and item construction or format (20, 21, 26). The Relapse Assessment for Schizophrenia Patients (RASP) is a six-question instrument (see Table 1A) that was developed to assess risk of impending relapse. The brevity of the instrument, ease of scoring, and the ability to administer with little or no supervision allows for routine administration and assessment of relapse risk by clinicians in a variety of treatment settings. Here we describe development of the RASP, as well as its psychometric properties among patients with schizophrenia.

Methods

RASP Development

RASP was developed by a steering committee of experts in psychiatric practice, schizophrenia treatment research, and psychometrics. Instrument development initiated with a systematic literature review (SLR) assessing drivers and measures of relapse risk in patients with schizophrenia to identify domains and items for inclusion in the RASP. The SLR was conducted in the Medline (PubMed) database using the following search terms as well as synonyms of the same:

- "schizophrenia," AND
- "relapse," "hospitalization," or "community tenure," AND
- "risk factors," "predictor," or "covariate" OR "medication adherence," "medication compliance," "medication persistence."

An item pool across multiple measurement domains was generated based on the manuscripts returned by the SLR. The first iteration of the questionnaire, a subset (k=22 items) of the item pool, was field tested and used as the source for items for the final screener that contained k=6 items. Item reduction, guided by the results of psychometric analyses, was performed in two steps. At each step, items that had the weakest psychometric properties or were redundant with other items were considered for elimination. During step 1, k=11 items were deleted leaving 11 (see Table 1B) of the original 22 items that showed the best reliability and validity

Table 1B Relapse Assessment for Schizophrenia Patients: k=11 Items

Item Number	Item Language	Final Disposition*
1	I've been feeling more worried or nervous than usual.	R
2	I've been feeling more restless or tense than usual.	R
3	I've been feeling more angry or irritable than usual.	R
5	I've had trouble getting along with family or friends lately.	D
6	I've been staying away from others more than usual.	R
8	I've been getting too little sleep.	R
10	Something specific happened recently that really upset me.	R
14	Just like people sometimes do, I have missed taking my medication at least once in the past week.	D
16	I have an emotional or mental health problem.	D
17	I need to take medication or be treated for an emotional or mental health problem.	D
22	How many days in the past week have you taken street drugs?	D

*Final Disposition: D=deleted as part of item reduction; R=retained after item reduction. From an initial extensive list, 11 items were identified that were considered to be of primary importance in determining whether patients were at risk for relapse. A further assessment reduced the list to 6 items that were considered critical for asessing patient relapse risk.

and were considered by the steering committee to be of primary importance in relapse risk. In step 2, the k=11 reduced item set was analyzed again, and item reliability and validity guided further item reduction and identification of the final set of k=6 items. The final set of k=6 items was considered critical for assessing relapse risk, had good face validity based on responses from patients in the pilot sample, and was the smallest set of items that retained good psychometric properties (see Table 1B). The k=6 items on the final RASP were binary (yes/no) and converted to a checklist response format.

The k=6 items retained for the final RASP screener fall into two domains, both of which measure recent (prior week) experiences and behaviors. The first set of 3 items assesses increase in anxiety symptoms while the second set of 3 items assesses change in social isolation and general emotional disturbance. Patients were instructed to endorse those items that were true during the prior week. Endorsement of any 3 of the 6 items indicates an increased risk of patient relapse.

Study Design

The study included the following three survey administrations: baseline, 3 months, and 6 months. The k=22 item questionnaire was administered as a monitored self-report (paper and pencil test) to a convenience sample of patients with schizophrenia (n=166) receiving care at one of three participating community mental health centers. The Positive and Negative Syndrome Scale (PANSS) (27) was administered after the administration of the RASP at each survey data point. A chart review was completed approximately ten months after the baseline administration for two sites on a subsample (n=81) of the larger study sample to identify relapse events during the entirety of the 9-month measurement period in addition to the 6-month period preceding the patients' baseline survey administration.

Study participants were recruited and data were collected between June 2, 2014 and December 31, 2015. All participants were required to have a diagnosis of schizophrenia, as identified by an *International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM)* code of 295.xx, or *Tenth Edition* of F20, currently treated with an antipsychotic medication, and not to be in an acute psychotic episode at the time of enrollment and baseline survey administration. Additionally, participants had to be ≥18 years of age and without brain disease other than their psychotic disorder. Each prospective participant was presented with an informed consent package. This study was approved by the Chesapeake Institutional Review Board. The PANSS rater collected completed informed consent before the participants' baseline survey administration and ensured that the participant understood fully the implications of participation. Upon completion of the informed consent form, study participants were handed the k=22 item version of the RASP and a pencil and asked to read the instructions and complete the form independently to the best of their ability. Participants were also instructed to ask for assistance if they needed help understanding the completion instructions given on the k=22 item version of the RASP.

Measures

The k=22 item version of the RASP was used for data capture. Most of the results reported here were of the psychometric evaluation focused on the reliability and validity of the k=6 item RASP. In addition to the RASP, the following measures were administered:

Positive and Negative Syndrome Scale (PANSS)

The PANSS interview, which lasted approximately 45 minutes, included three sections: positive symptoms, negative symptoms, and general psychopathology. The PANSS

was administered by a certified PANSS rater after completion of the RASP. Video-recorded PANSS sessions and PANSS forms were used for training and to examine inter-rater reliability.

Relapse

Relapse was assessed using data from three sources, including patient charts, crisis logs from one participating community mental health center, and change in PANSS scores. Relapse was calculated for cases on which patient charts were provided. As charts alone underestimated relapse, change in PANSS score was added as an additional source of relapse to reduce the probability of false negatives. Though crisis logs were available for one site, the data were redundant with the combination of the other two sources.

First, full psychiatric patient charts including all entries for the study period were provided by five of seven study sites and were reviewed for evidence of relapse by chart review technicians. Any indication of psychiatric hospitalization, psychiatric emergency department use, or police action as a result of psychotic or self-harm behavior was considered an indication of relapse. Additionally, one site allowed access to a crisis log as a supplement to the charts. Any report from a case manager or clinical or residential staff of psychiatric emergency or inpatient service utilization, relapse to drug or alcohol use, police action, or residential disruption or recent homelessness secondary to exacerbation of psychotic symptoms was coded as relapse. Finally, positive symptom exacerbation, defined as an increase in total PANSS Total Score ≥15 points (28), was coded as relapse. The type of evidence as well as the date were coded and entered into the study database. Additionally, an increase in the score of any of six positive symptom items (P1, P2, P3, P6, P7, and G8) to a score ≥5 if the previous score was ≤3 or ≥6 if the previous score was 4 (29) was coded as a relapse.

Analyses

There were two steps in reducing the number of items from k=22 to the minimum number that retains most of the good psychometric properties. The psychometric analysis of the RASP was based on data collected using the k=22 item version. During step 1, relying on the results of the analysis, including content validity, test-retest reliability, internal consistency, construct validity, and concurrent validity, the number of items was reduced to k=11. During step 2, the psychometric analyses were repeated on the k=11 item set, which led to further item reduction and identification of the final k=6 item screener. The psychometric properties of the k=6 item version are described. All analyses reported here, with the exception of content validity, are reported only for the final RASP screener (k=6).

Table 2 Demographic and Baseline Characteristics by Site

Characteristic	Site A N=83	Site B N=27	Site C N=56
Age, mean (SD)	52 (11)	48 (14)	47 (12)
Male, n (%)	57 (69)	20 (74)	35 (63)
Ethnicity, n (%)			
African American	77 (93)	9 (33)	27 (48)
Asian/Pacific Islander	1 (1)	1 (4)	0
Other	0	2 (7)	1 (2)
White	3 (4)	15 (56)	28 (50)
Not reported	2 (2)	0	0
Baseline scores			
PANSS Total Score, mean (SD)*	61.95 (12.73)	62.41 (14.32)	51.21 (15.86)
RASP Total Score, mean (SD)	2.88 (2)	1.63 (1.8)	1.98 (1.87)

*p<.05, post hoc test indicates that Site C is different from both Sites A and B. PANSS=Positive and Negative Syndrome Scale; RASP=Relapse Assessment for Schizophrenia Patients.

Content Validity

Face validity of the RASP was established by the steering committee of experts as well as the pilot sample of patients with schizophrenia (n=6) recruited from one of the study sites. After completing the 22-item version of the RASP, pilot participants were interviewed using a cognitive debriefing form. The focus of the debriefing interview was the clarity, meaning, and intelligibility of RASP items, response arrays, and the instructions. Overall survey burden, including item difficulty, instrument length, and fatigue, was also assessed.

Internal Consistency and Item Behavior

The homogeneity of the RASP was assessed using Cronbach's alpha because it is the traditional metric of internal consistency and measures how closely items are related to one another. Alpha can range from 0 to 1, with a higher value indicating greater item relatedness. Typically, a scale is considered reliable if its Cronbach's alpha coefficient exceeds 0.70. While it is desirable that the screener measures multiple factors (domains), separate factors may not correlate with each other, in which case alphas are reported for each factor. Item characteristic curves (ICC) were used to evaluate the contribution of each item to the discrimination ability of the RASP as a whole; steeper slopes indicate greater contribution of the item to the discrimination ability of the RASP.

Test-Retest Reliability

Test-retest reliability of the RASP was assessed using measures of agreement on responses collected from a sub-

Table 3 Rotated Factor Pattern with Standardized Regression Coefficients for Two Factors (N=166)

Item	Question	Increased Anxiety	Social Isolation
1	I've been feeling more worried or nervous than usual.	0.8579	-0.0611
2	I've been feeling more restless or tense than usual.	0.8249	-0.0153
3	I've been feeling more angry or irritable than usual.	0.6054	0.2619
4	I've been staying away from others more than usual.	-0.1524	0.8863
5	Something specific happened recently that really upset me.	0.1257	0.6243
6	I've been getting too little sleep.	0.2293	0.6236

sample (n=13) who retook the RASP three days after baseline. The kappa coefficient, which controls for chance agreement between the test response and the retest response, was calculated for each item, each factor, and total RASP scores.

Construct Validity

Principal components analysis was used to determine the presence of multiple underlying latent constructs in the RASP. Oblique rotation allowed for items to load on as few factors as possible while allowing the factors to correlate with each other. (Note: oblique rotation is an alternative to one of the many orthogonal rotation routines that require the underlying factors to be uncorrelated with each other.) Eigenvalue cutoff and scree plot analysis guided selection of the number of factors. Factors were labeled based on the content of items that loaded on each.

Concurrent Validity

Simultaneous administration of the PANSS and the RASP was used to assess concurrent validity. Pearson zero-order correlation coefficients at the item, subscale, and survey levels were calculated to estimate the direction and strength of the relationship between the RASP and PANSS. The PANSS was scored using Marder scoring (30). To facilitate ease of scoring and interpretation, RASP subscale and total scores were calculated using unit weight scoring (each item scored as a 1 if endorsed) instead of weighted or factor scores. The baseline data point served for the primary concurrent validity calculation.

Sensitivity to Change

To estimate its ability to detect change in relapse risk, change in RASP score was compared with change in PANSS score over time. Because this is a single group observational study with the expectation that cases will change by truly different amounts, a simple correlation method is an acceptable metric for estimating sensitivity to change (31). Change scores from baseline to month 3, then again from month 3 to month 6, were calculated for both the RASP and PANSS total and subscale scores. The estimate of sensitivity is presented as the person zero-order correlation coefficient between the RASP and PANSS change scores for the same time period.

Criterion Validity

The RASP raw scores were compared with evidence of relapse documented in patient charts, the crisis log from one site, and an increase PANSS Total Score ≥15 (28), as well as an exacerbation of specific positive symptom items (29). Multiple RASP scoring protocols were investigated, including endorsement of 1, 2, 3, or 4 items. A maximum lag of three months was allowed between the RASP administration and evidence of relapse. Agreement was calculated between RASP at baseline and relapse status within the three months after baseline and corrected for chance agreement using kappa.

Results

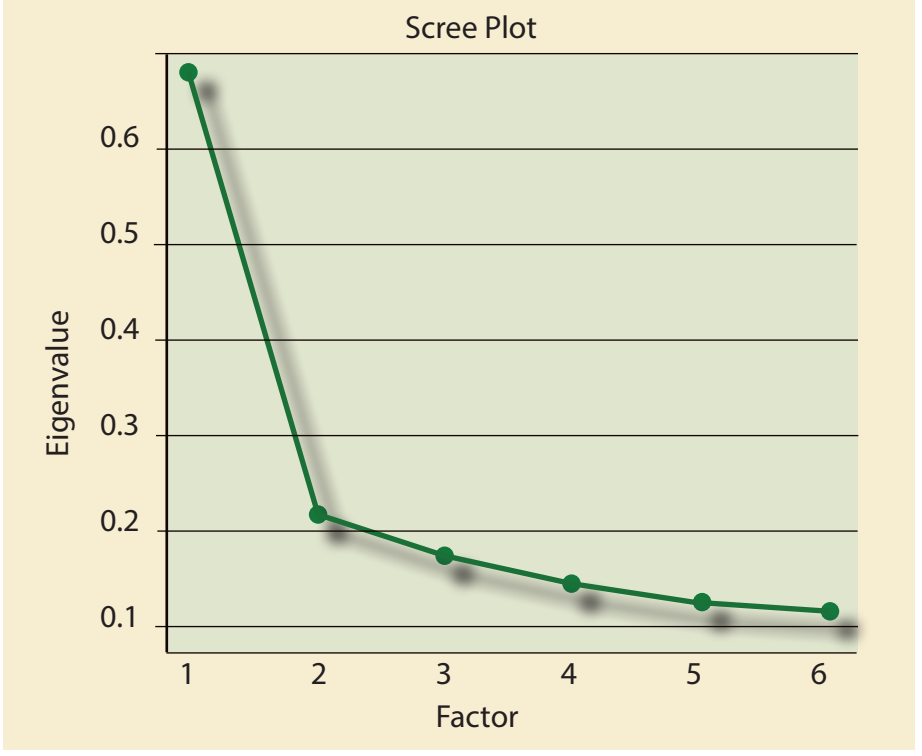
Descriptive Statistics

A summary of the demographic and baseline characteristics for study participants from each of the three participating mental health facilities is provided in Table 2. Of note is that the three sources of cases were different on PANSS Total Score at baseline. Site C was lower in PANSS Total Score than was Site A or B. However, there was no difference between sites on number of cases that required assistance to complete the RASP (χ^2=2.86, df=2, NS).

Item Reduction

In an attempt to reduce the item set to the minimum number that retained or improved on the properties of the k=22 item version, the psychometric properties of the instrument and items were examined. In step 1, test-retest reliability, internal consistency, factor analysis, and concurrent validity led to elimination of k=11 items from the k=22 item version. In step 2, psychometric analyses were repeated for the k=11 reduced items set (see Table 1A). Three of 11 items loaded on the Increased Anxiety factor, and all correlated either strongly or very strongly with the PANSS Anxiety/Depression and Excitement subscales and PANSS Total Score and had acceptable psychometric properties. The relationship between k=5 of 11 item that loaded onto the Social Isolation factor and PANSS scales was less clear, with items correlating with 1 or more of the following PANSS scales: 1) Excitement and Anxiety/Depression, 2) Anxiety/Depression, 3) Positive Symptom, and 4) Total Score. Of the

Figure 1 Six-Item Scree Plot



balance of the k=11 items, 1 item (item 5) did not correlate with any of the PANSS scales. Furthermore, some items were redundant, had low endorsement, low ICC slopes, or only loaded to 1 factor, making them good targets for deletion. After eliminating these items, k=6 items that correlated well with the PANSS and had strong psychometric properties were retained in the final instrument.

Psychometric Properties of the RASP

Following item reduction described above, the RASP consisted of k=6 questions (see Table 1B). The balance of this report focuses on the k=6 item screener, which was renumbered consecutively 1 to 6.

Content Validity

During pilot testing, there was high concordance between all participant comments. Pilot results indicated all k=6 items were understood correctly by all pilot participants, with no suggested alternative wordings.

Construct Validity: Principal Components

Principal components analysis was used to determine the presence of multiple underlying latent constructs in the RASP data. Evaluation of eigenvalues and the scree plot (see Figure 1) revealed a natural cutoff value of .20, supporting the selection of two factors. Principle components were rotated using an oblique method, and the standardized regression coefficient (rotated pattern) indicated that all loadings were at or above 0.60 for both factors (see Table 3). The Increased Anxiety factor included items 1, 2, and 3, while the factor for Social Isolation included items 4, 5, and 6. These factors are in line with known drivers of relapse (e.g., increased anxiety, social isolation) (32, 33). Subscales based on factor loading pattern were scored using unit weighting. Items 1, 2, and 3 were summed (i.e., counted the number of items [0–3] that were endorsed) as an Increased Anxiety subscale, and items 4, 5, and 6 for a Social Isolation subscale score. The balance of psychometric analysis presented here focused on individual items, subscale scores (unit weighted), and total screener score (unit weighted).

Reliability: Test-Retest

Test-retest reliability ranged from strong (item 1 kappa=0.65) to modest (item 2 kappa=0.30) for individual RASP items. Test-retest for unit weighted factor scores were moderate for the Increased Anxiety subscale (kappa=0.42) and Social Isolation subscale (kappa=0.39); the reliability for the unit weighted total scale score was strong (kappa=0.67).

Reliability: Internal Consistency and Item Behavior

Cronbach's alpha for items within the screener was 0.77, indicating high-item relatedness assuming a single-factor screener. Items within the Increased Anxiety subscale had a Cronbach's alpha of 0.72, a level that also indicates good internal consistency within that factor. Items within the Social Isolation subscale had a Cronbach's alpha of 0.62. Although acceptable, this lower alpha may be due to the broader scope of the items composing Social Isolation. The Cronbach's alpha of 0.69 between Increased Anxiety and Social Isolation subscales (see Table 4) was somewhat higher than expected and may indicate that the two factors are related constructs within the population of patients with schizophrenia.

Table 4 Cronbach's Alpha for Two-Factor Model Screener at Baseline (N=166)

	Cronbach's Alpha
Among items	0.77
Among factors	0.69
Within factors	
Increase in Anxiety	0.72
Social Isolation	0.62

Item response curves were used to examine the ability of scale items to differentiate patients that vary along the latent trait as measured by each item. Curves indicate the probability that a patient with a given level of the trait will endorse the item (for items with binary responses) or give a specific answer (for items with continuous or multiple possible responses). Item slopes ranged from 1.236 to 3.1776, with an average of 2.036 (see Table 5), indicating a very high contribution of each item to the whole of the RASP instrument's ability to differentiate.

Concurrent Validity

Pearson zero-order correlation coefficients were calculated for the unit weighted score for the two subscales and RASP Total Score compared with the PANSS subscales and Total Score (see Table 6). The Increased Anxiety subscale correlated modestly (r=.19) with the PANSS Positive Symptom scale, moderately (r=.26) with the Excitement scale, strongly (r=.53) with the Anxiety scale, and moderately (r=.25) with the PANSS Total Score. The Social Isolation subscale score correlated modestly (r=.19) with the PANSS Positive Symptom scale, moderately (r=.24) with the Excitement scale, a bit stronger (r=.36) with the Anxiety scale, and moderately (r=.24) with the Total Score. The RASP Total Score correlated moderately (r=.22) with the PANSS Positive Symptom and the Excitement scale (r=.29), strongly (r=.51) with the Anxiety scale, and moderately (r=.28) with the PANSS Total Score.

Sensitivity to Change

To estimate its ability to detect change in relapse risk, change in RASP scores were compared with change in PANSS scores over time. Change scores were calculated for both the RASP raw scores and PANSS from baseline to month 3, then again from month 3 to month 6. The estimate of sensitivity is presented as Pearson zero-order correlation coefficients between RASP and PANSS change scores that span the same time period. Change in RASP Increased Anxiety subscale and the PANSS Anxiety scale from baseline to month 3 correlated moderately and positively (r=.32, p<.01), and change in RASP Total Score correlated with PANSS Total Score (r=.26, p<.01). Similarly, change from month 3 to month 6 in RASP Increased Anxiety subscale and PANSS Anxiety scale correlated moderately (r=.35, p<.01).

Table 5 Two-Factor Model Item Characteristic Slopes at Baseline from Highest Discrimination to Lowest (N=166)

Item	Question	Slope Estimate	Standard Error	P
3	I've been feeling more angry or irritable than usual.	3.177	0.93471	0.0003
6	I've been getting too little sleep.	2.16404	0.5228	<0.0001
2	I've been feeling more restless or tense than usual.	2.13903	0.48902	<0.0001
1	I've been feeling more worried or nervous than usual.	2.10362	0.47859	<0.0001
5	Something specific happened recently that really upset me.	1.39814	0.32594	<0.0001
4	I've been staying away from others more than usual.	1.23564	0.2957	<0.0001

Table 6 Two-Factor Model Correlation with PANSS at Baseline (N=166)

Factor	PANSS	Negative	Positive	Disorganized	Excitement	Anxiety	Total
Increased Anxiety	Pearson Correlation	-0.074	0.1885	0.1199	0.2619	0.5324	0.2502
	P	0.3437	0.015	0.124	0.0007	<0.0001	0.0011
Social Isolation	Pearson Correlation	-0.0076	0.189	0.1178	0.2392	0.3557	0.2348
	P	0.9228	0.0148	0.1306	0.0019	<0.0001	0.0023
Total RASP	Pearson Correlation	-0.048	0.21573	0.1359	0.28694	0.51152	0.27759
	P	0.5388	0.0052	0.0808	0.0002	<0.0001	0.0003

PANSS=Positive and Negative Syndrome Scale; RASP=Relapse Assessment for Schizophrenia Patients.

Criterion Validity: Relationship Between RASP and Relapse

The relationship between the RASP and relapse was estimated using a 2X2 cross tabulation agreement table of RASP score at baseline and evidence of relapse at either baseline or month 3. One of the sources of relapse data was patient charts. There was a difference in the change in PANSS Total Score baseline to 3 months between cases with charts (X=-5.39; SD=16.47) versus those for whom charts were unavailable (X=3.67; SD=12.89) ($p<.05$), though the magnitude of these differences is not clinically relevant (28). The relationship between RASP score and subscale scores and the two sources of relapse data at baseline were as expected. As mentioned earlier, chart data underrepresented relapse rate (4%) and was, therefore, augmented with PANSS score (30). Though all correlations were directionally correct (see Table 7), the strongest correlations were between PANSS and the RASP total and subscale scores and total relapse and all RASP scores (all p's<.05).

Endorsement of items on the RASP was used to group cases into high versus low risk of relapse. The following four RASP scoring algorithms were tested: 1) ≥1 item endorsed, 2) ≥2 items endorsed, 3) ≥3 items endorsed, and 4) ≥4 items endorsed. Evidence of relapse was determined from patient charts, site crisis logs, or an increase in PANSS scores. Agreement between evidence of relapse and each RASP scoring algorithm was used to evaluate the relative strength of each algorithm and is reported in Table 8. At Time 0 (baseline), comparison of four different scoring algorithms indicated that endorsement of either ≥1 or ≥2 items (66% and 52%, respectively) likely overestimated 3-month relapse risk, while endorsement of either ≥3 or ≥4 items (33% and 23%, respectively) returned estimates that are more consistent with expectations. When used to calculate agreement with relapse, endorsement of either ≥1 or ≥4 items returned lower percentage agreement (59% and 70%, respectively). The kappa statistic of agreement was similar for endorsement of either ≥2 or ≥3 items (.476 and .474, respectively), while it was considerably lower for either ≥1 or ≥4 items (.279 and

Table 7 Agreement Between RASP Total and Subscale Scores and Sources of Relapse Data

Pearson Correlation Coefficients Between RASP Total and Subscales and Sources of Relapse Data (N=79)
Probability > |r| under H0: Rho=0

	Baseline Total RASP	Baseline Anxiety Subscale	Baseline Social Subscale
Baseline Chart	0.14272	0.18648	0.18179
	0.2096	0.0999	0.1088
Baseline PANSS Relapse	0.4292	0.46084	0.25704
	<.0001	<.0001	0.0231
Any Relapse	0.47454	0.5097	0.3281
	<.0001	<.0001	0.0032

PANSS=Positive and Negative Syndrome Scale; RASP=Relapse Assessment for Schizophrenia Patients.

Table 8 Comparison of RASP Scoring Algorithms: Cases at Elevated Risk and Agreement with Relapse (N=79)

	f At Risk	% At Risk	% Agreement	Kappa
RASP ≥1	52	65.82	59.49	0.2794
RASP ≥2	41	51.90	73.42	0.4762
RASP ≥3	26	32.91	77.22	0.4737
RASP ≥4	18	22.78	69.62	0.2274

RASP=Relapse Assessment for Schizophrenia Patients.

.227, respectively). Although there is little difference in percent agreement and kappa between endorsement of either ≥2 or ≥3 items, the percentage of cases that met criterion for elevated risk using the ≥3 item endorsement criterion is more consistent with expectations (52% vs. 33%, respectively). Therefore, the ≥3 item endorsement scoring criterion was employed for calculating criterion validity.

The overlap between those who evidenced relapse and those at elevated risk based on the RASP is the centerpiece of the screener's ability to detect imminent relapse. Table 8A shows agreement between RASP ≥3 (n=26, 33%) and evidence of relapse based on chart data, crisis log, increase in ≥15 points on the PANSS Total Score, or increase in severity on ≥1 on 6 PANSS positive items. Within this analysis, there were 24 (30%) relapses between baseline and month 3 data points. The RASP correctly predicted 61 cases (77%). Sensitivity (67%), specificity (82%), positive predictive power (63%), and negative predictive power (85%) were all acceptable to good (see Table 8B). Agreement, as measured by kappa, was also good (k=.47, p<.05).

Table 8A Agreement Between RASP Predicted Relapse (Rows) and Relapse Based on Chart Data, Crisis Log, and PANSS (Columns) (N=79)

		Relapse Charts, Crisis Log, and PANSS			
		y	n	Total	Total/N*
RASP ≥3	y	16	10	26	33%
	n	8	45	53	67%
	Total	24	55	79	
	Total/N*	30%	70%		77%

PANSS=Positive and Negative Syndrome Scale; RASP=Relapse Assessment for Schizophrenia Patients. *N=79.

Table 8B Agreement Statistics

kappa	0.474
ASE	0.106
95% lower confidence limit	0.266
95% upper confidence limit	0.682
Sensitivity	67%
Specificity	82%
Positive predictive power	62%
Negative predictive power	85%

ASE=alpha's standard error.

Discussion and Conclusions

Although proper treatment can reduce the symptoms of schizophrenia, relapse to active psychosis is likely at a rate of 3.5% per month, even with properly managed symptoms (34). The probability of relapse can be as high as 80% within twelve months when treatment is intermittent, highlighting the importance of close monitoring and management of schizophrenia symptoms (35). Currently, tools designed to identify patients with schizophrenia at elevated risk for relapse that can be easily and inexpensively used in clinical settings are few. A brief PRO tool that can be completed independently by most patients with schizophrenia in a clinical setting is clearly needed. The RASP was designed to fill this need.

The RASP adds to the currently available battery of screeners for schizophrenia, but provides several new features. For example, several instruments designed to assess psychiatric disease severity have been used to track the likelihood of relapse among psychiatric patients. By contrast, the RASP was designed specifically to assess the risk of relapse among patients with schizophrenia. Other tools—such as diagnostic interviews—require trained raters, whether they are time intensive (e.g., Schedule for Affective Disorders and Schizophrenia, PANSS, Brief Psychiatric Rating Scale) or brief (Global Assessment of Functioning, Clinical Global Impression-Severity scale), limiting their use in clinical practice. Finally, currently available self-report tools that assess treatment benefits, such as the Schizophrenia Quality of Life Scale (36) or the Social Adjustment Scale (37), can be lengthy (10 items or more) and do not assess relapse risk. Development of the 6-item RASP and a description of its psychometric properties as a self-report relapse prediction tool was the purpose of this study.

A pilot sample of patients with schizophrenia indicated that the scale has good content validity, as patients were able to describe in their own words the meaning of each of the 6 items with no recommendations for revision. Test-retest reli-

ability, internal consistency, and item response curves were all acceptable. Furthermore, concurrent validity results indicated that RASP scores are more strongly related to Anxiety, Excitement, and PANSS Total Score than to the Positive Symptom scale. This finding is consistent with the theoretical approach essential to development of the RASP of measuring symptoms that precede psychotic relapse. It is supposed to measure prodromal symptoms that appear before the exacerbation of positive symptoms, which themselves may be the manifestation of, rather than predictive of, relapse. Even though not strongly correlated with positive symptoms, RASP Total Score significantly predicted relapse as measured using patient chart data, crisis logs, and exacerbation of symptoms based on PANSS Total Score and positive symptom items, lending additional support to the development of a relapse screener that does not directly measure positive psychotic symptoms. Although sensitivity (67%) indicates that approximately one-third of patients at risk for relapse are not detected by the RASP and positive predictive power (62%) indicates that approximately one-third of those identified at elevated risk may not be at risk of imminent relapse, in a clinical setting where several other modes of clinical assessment are typically employed the RASP adds measurement and potentially detection of relapse risk not otherwise available. An increase in sensitivity to, and positive predictive power of, a patient's risk compared with standard clinical practice without such a PRO instrument may provide an advantage in overall clinical care.

Instrument development, item reduction, and calculation of psychometric properties were performed using orthodox procedures; however, there are some methodological limitations. Content validity was assessed using a small sample of pilot cases (n=6) and test-retest reliability was assessed on a small sample (n=13) as well. Both should be replicated using larger samples and potentially a broader range of symptom severity. Also, participants in the study completed the RASP every three months (baseline, 3-month and 6-month assessments), which is less frequent than it was designed to be used (e.g., monthly). Further evaluation of the RASP is needed to estimate response variation and criterion validity with shorter periods between assessments.

The population from which this sample was drawn may not be fully representative of the more general population of patients with schizophrenia. Patients whose charts were included in the analysis had a slight positive change in PANSS while those without charts had a slight decrease in PANSS from baseline to month 3. Similarly, there were some differences in baseline total PANSS between sites, which may indicate a difference in severity. However, the proportion of cases requiring assistance completing the RASP was similar across sites. If the patients in the sample were higher functioning compared with most patients with schizophrenia, their ability to complete the screener may not be generalizable to the larger population of patients with schizophrenia. As such, it is not clear at what level of schizophrenia severity the reliability of self-report on the RASP becomes unacceptably low. Finally, measurement of relapse included the following multiple proxies: 1) review of patient charts indicating hospitalization, psychiatric emergency department visit, police involvement, 2) increase in PANSS Total Score by more than 15 points (38, 39), 3) evidence of a relapse event from a crisis log kept by one study site, and 4) evidence of symptom exacerbation as indicated by increase in score on positive symptom items from the PANSS (29). Evidence of relapse between baseline and month 3 based on events gleaned from charts was likely underrepresented (4%), while when augmented with increases in PANSS scores may have overrepresented relapse (30%). However, this range is not inconsistent with the same reported elsewhere (34, 35). Measurement of relapse based on specific purpose or application would be helpful. For example, if used to identify potential hospitalization as part of a readmission reduction program, claims data might provide a more relevant proxy of relapse. Further, precedence indicates that collateral report of relapse as well as other constructs could possibly provide additional valuable information concerning schizophrenia patient behavior and relapse status. Nevertheless, all data sources that produce proxies of schizophrenia relapse have limitations. Matching those limitations to the needs of the instrument is essential to estimate its performance. Finally, it is unclear how the RASP will be used by clinicians to plan or modify treatment.

Although it was designed for use in a clinical setting, the RASP may have application in other settings, such as assessing relapse risk in observational studies or randomized controlled trials. Because of the association between relapse events and hospitalizations, the RASP may also have utility in predicting increased risk of hospitalization. Although the RASP can provide an overview of patients' current level of disease severity, its aim is to identify changes in an individual patient's risk of relapse; therefore, repeated use of the screener is recommended to maximize relapse risk monitoring. The RASP can be completed by most patients with schizophrenia within five minutes without significant aid. The brief nature of the screener, along with its simple scoring instructions, allows it to be employed in a variety of environments, including physician office visits, case manager visits, and structured day programs.

In summary, the RASP is a self-report tool for assessing risk of relapse for patients with schizophrenia. The reliability and validity data presented here, including RASP's relationship to PANSS scores and relapse over the study period, support the use of this instrument in settings where a

brief self-report assessment of relapse risk among patients with schizophrenia may be of benefit. Because the RASP is a patient self-report screener with minimal patient burden and low item difficulty, it requires no training to administer and monitor. The brevity of the form, ease of scoring, and the ability to administer with little or no supervision allows for routine administration and assessment of relapse risk.

Note: The RASP is the result of a work sponsored by Otsuka Pharmaceutical Development & Commercialization, Inc. and H. Lundbeck A/S. Otsuka Pharmaceutical Development & Commercialization, Inc. owns intellectual property of the RASP, including but not limited to all and any translations and other derivatives (e.g., electronic versions). Otsuka Pharmaceutical Development & Commercialization, Inc. has assigned Mapi Research Trust for the management of the instrument licenses and permission to use. Please consult the Mapi Research Trust website at www.proqolid.org.

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References

1. Rajagopalan K, O'Day K, Meyer K, Pikalov A, Loebel A. Annual cost of relapses and relapse-related hospitalizations in adults with schizophrenia: results from a 12-month, double-blind, comparative study of lurasidone vs quetiapine extended-release. J Med Econ 2013;16(8):987-996.
2. Olivares JM, Sermon J, Hemels M, Schreiner A. Definitions and drivers of relapse in patients with schizophrenia: a systematic literature review. Ann Gene Psychiatry 2013;12(1):32.
3. Ascher-Svanum H, Zhu B, Faries D, Salkever D, Slade E, Peng X, et al. The cost of relapse and the predictors of relapse in the treatment of schizophrenia. BMC Psychiatry 2010;10(1):2.
4. Doering S, Muller E, Kopcke W, Pietzcker A, Gaebel W, Linden M, et al. Predictors of relapse and rehospitalization in schizophrenia and schizoaffective disorder. Schizophr Bull 1998;24(1):87-98.
5. Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. BMC Psychiatry 2008;8:32.
6. Alvarez-Jimenez M, Priede A, Hetrick SE, Bendall S, Killackey E, Parker AG, et al. Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies. Schizophr Res 2012;139(1-3):116-128.
7. Higashi K, Medic G, Littlewood KJ, Diez T, Granstrom O, De Hert M. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. Ther Adv Psychopharmacol 2013;3(4):200-218.
8. Haddad PM, Brain C, Scott J. Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. Patient Relat Outcome Meas 2014;5:43-62.
9. Robinson D, Woerner MG, Alvir JM, Bilder R, Goldman R, Geisler S, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 1999;56(3):241-247.
10. Boyer L, Millier A, Perthame E, Aballea S, Auquier P, Toumi M. Quality of life is predictive of relapse in schizophrenia. BMC Psychiatry 2013;13:15.
11. Emsley R, Chiliza B, Asmal L, Harvey BH. The nature of relapse in schizophrenia. BMC Psychiatry 2013;13(1):50.
12. Tibbo P, Malla A, Manchanda R, Williams R, Joober R. Relapse risk assessment in early phase psychosis: the search for a reliable and valid tool. Can J Psychiatry 2014;59(12):655-658.
13. Butzlaff RL, Hooley JM. Expressed emotion and psychiatric relapse: a meta-analysis. Arch Gen Psychiatry 1998;55(6):547-552.
14. Durham RC, Allan T, Hackett CA. On predicting improvement and relapse in generalized anxiety disorder following psychotherapy. Br J Clin Psychol 1997;36 (Pt 1):101-119.
15. Cavelti M, Kvrgic S, Beck EM, Kossowsky J, Vauth R. Assessing recovery from schizophrenia as an individual process. A review of self-report instruments. Eur Psychiatry 2012;27(1):19-32.
16. Bell M, Fiszdon J, Richardson R, Lysaker P, Bryson G. Are self-reports valid for schizophrenia patients with poor insight? Relationship of unawareness of illness to psychological self-report instruments. Psychiatry Res 2007;151(1-2):37-46.
17. Atkinson M, Zibin S, Chuang H. Characterizing quality of life among patients with chronic mental illness: a critical examination of the self-report methodology. Am J Psychiatry 1997;154(1):99-105.
18. Dickinson D, Bellack AS, Gold JM. Social/communication skills, cognition, and vocational functioning in schizophrenia. Schizophr Bull 2007;33(5):1213-1220.
19. Gaebel W, Riesbeck M, von Wilmsdorff M, Burns T, Derks EM, Kahn RS, et al. Drug attitude as predictor for effectiveness in first-episode schizophrenia: results of an open randomized trial (EUFEST). Eur Neuropsychopharmacol 2010;20(5):310-316.
20. Zung WW. A rating instrument for anxiety disorders. Psychosomatics 1971;12(6):371-379.
21. Herz MI, Lamberti JS, Mintz J, Scott R, O'Dell SP, McCartan L, et al. A program for relapse prevention in schizophrenia: a controlled study. Arch Gen Psychiatry 2000;57(3):277-283.
22. Millier A, Clay E, Charaf I, Chauhan D, Murthy V, Toumi M, et al. Patient reported outcomes instruments in schizophrenia: a review of psychometric properties. Open J Med Psychol 2014;3(2):141-156.
23. Buss AH, Perry M. The aggression questionnaire. J Pers Soc Psychol 1992;63(3):452-459.
24. Bodlund O, Kullgren G, Ekselius L, Lindstrom E, von Knorring L. Axis V—Global Assessment of Functioning Scale. Evaluation of a self-report version. Acta Psychiatr Scand 1994;90(5):342-347.

25. Beck EM, Cavelti M, Wirtz M, Kossowsky J, Vauth R. How do socio-demographic and clinical factors interact with adherence attitude profiles in schizophrenia? A cluster-analytical approach. Psychiatry Res 2011;187(1-2):55-61.

26. Beck EM, Cavelti M, Kvrgic S, Kleim B, Vauth R. Are we addressing the 'right stuff' to enhance adherence in schizophrenia? Understanding the role of insight and attitudes towards medication. Schizophr Res 2011;132(1):42-49.

27. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13(2):261-276.

28. Hermes ED, Sokoloff D, Stroup TS, Rosenheck RA. Minimum clinically important difference in the Positive and Negative Syndrome Scale with data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). J Clin Psychiatry 2012;73(4):526-532.

29. Markowitz M, Fu DJ, Levitan B, Gopal S, Turkoz I, Alphs L. Long-acting injectable paliperidone palmitate versus oral paliperidone extended release: a comparative analysis from two placebo-controlled relapse prevention studies. Ann Gen Psychiatry 2013;12(1):22.

30. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997;58(12):538-546.

31. Stratford PW, Riddle DL. Assessing sensitivity to change: choosing the appropriate change coefficient. Health Qual Life Outcomes 2005;3:23.

32. Lehman AF, Kreyenbuhl J, Buchanan RW, Dickerson FB, Dixon LB, Goldberg R, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. Schizophr Bull 2004;30(2):193-217.

33. Lieberman JA, Perkins D, Belger A, Chakos M, Jarskog F, Boteva K, et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. Biol Psychiatry 2001;50(11):884-897.

34. Csernansky JG, Mahmoud R, Brenner R, Risperidone USASG. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med 2002;346(1):16-22.

35. Emsley R, Oosthuizen PP, Koen L, Niehaus DJ, Martinez G. Symptom recurrence following intermittent treatment in first-episode schizophrenia successfully treated for 2 years: a 3-year open-label clinical study. J Clin Psychiatry 2012;73(4):e541-547.

36. Isjanovski V, Naumovska A, Bonevski D, Novotni A. Validation of the Schizophrenia Quality of Life Scale Revision 4 (SQLS-R4) among patients with schizophrenia. Open Access Maced J Med Sci 2016;4(1):65-69.

37. Gameroff MJ, Wickramaratne P, Weissman MM. Testing the Short and Screener versions of the Social Adjustment Scale-Self-report (SAS-SR). Int J Methods Psychiatr Res 2012;21(1):52-65.

38. Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry 2005;162(3):441-449.

39. Correll CU, Kishimoto T, Nielsen J, Kane JM. Quantifying clinical relevance in the treatment of schizophrenia. Clin Ther 2011;33(12):B16-39.