Paranoia in The Prodroma of Psychosis

James Wilcox 1, David Briones 2, Syed Quadri 3,

1 University of Washington

2 Texas Tech University Health Sciences Center

3 University of Arizona

James Wilcox, M.D., PhD is corresponding author James.Wilcox2@VA.gov

**Abstract:**

This study examines a group of 320 young people with the new onset of psychiatric symptoms and evaluates factors which may lead to psychotic changes. Prodromal subjects were screened for symptoms and later given the Structured Clinical Interview of DSM-III-R (SCID) at one year, two years and five years post onset. We also administered the Ideas of Reference Interview Scale (IRIS) and the Paranoia Scale (PS) at each evaluation. Our analysis found that the use of the PS and IRIS enhanced prediction of conversion to psychosis and long term prognosis. The early occurrence of ideas of reference appears to predict conversion to psychosis. Once full psychosis had developed, paranoia tended to predict relatively good prognosis with less personality deterioration over time. This suggests that while unusual thinking may be predictive of conversion to psychosis, the type of delusion (paranoid vs. disorganized) is a strong indicator of continued deterioration over time. This predictive value was preserved when considered among other high-risk variables.

Key words: psychosis, prodroma, paranoia, schizophrenia

**Introduction**

In recent years there has been increased interest in prognostic features of the schizophrenic prodroma, yet strongly predictive models have been difficult to formulate [1,2,3,4,5,6,7,8,9]. Several factors such as high genetic loading and substance abuse are associated with poor outcome for many patients, but are far from conclusive [2, 3, 4, 5, 6, 7]. Early onset of paranoia also appears to be linked to conversion into psychosis [8, 9,10]. By using operational criteria, the risk associated between early paranoia and outcome can be assessed with a high degree of validity. Paranoid thinking in schizophrenia has been associated with less personality deterioration over years of illness [6, 9, 12, 13,14,15,16]. Since both ideas of reference and other forms of paranoia are found in in a variety of situations [13, 14, 15, 16, 17], a complex analysis of variables is needed to determine which cases are most at risk for conversion to psychosis and which are likely to later experience deterioration of the personality. By inclusion of detailed scales with operational criteria we hoped to determine the value of risk factors for both early conversion and also the prediction of prognosis over time [ 18 ].

This study was designed to examine the effect of paranoia on both conversion and on long term prognosis. We also assessed the effects of symptomatic and demographic variables at onset of symptoms, and at one year, two year and five year intervals after the first observation of psychological impairment. The subjects were followed over the next five years. We concentrated on new cases of illness regardless of diagnosis and felt that the addition of operational scales would enhance prediction for both conversion and prognosis.

**Methods**

This was a prospective study of patients with new onset of psychiatric symptoms. These subjects were recruited from mental health clinics and hospitals in Western and Northern Texas. Appropriate permission was obtained from the Texas Tech University Institutional Review Board before the study began. All subjects gave informed consent to be interviewed. Subjects were at least 18 years old at the time of enrollment and were primarily English speaking. Each subject was screened to assess the presence of prodromal symptoms (these were essentially new onset of schizotypal symptoms of 6 months duration or less) by the author, JW. Patients were subsequently followed at intervals of one, two and five years. We screened 320 original subjects. We found that 87% of potential subjects agreed to participate, yielding over 200 subjects for the study. We collected information on family history, education, drug use and age of onset of psychiatric symptoms. Each subject was also interviewed using the Paranoia Scale (PS) [18], the Brief Psychiatric Rating Scale (BPRS) [19] the Ideas of Reference Interview Scale (IRIS), and the Structured Clinical Interview for DSM IIIR (SCID) [20].

Using this method of recruitment, we were able to enroll 278 subjects in the study. Follow up interviews using the PS, IRIS, SCID and BPRS were conducted one, two and five years after the initial assessment. All assessments were done by investigators JW and SQ. Kappa scores for reliability between the two raters was found to be high (.81). The mean age of new subjects was 22 years with a range of 18 to 29 years. Fifty two percent of the subjects were male. All subjects were in good physical health.

**Statistical analysis**

Analysis of findings used Chi square test and Student’s t test as appropriate. Pearson correlations were run to examine random correlations of possible interactions. Multiple regression analysis was performed to evaluate variation in effect of demographics, BPRS, PS, SCID and IRIS scores at one year, two years and five years to assess effects upon symptom variation over time. SCID findings at these intervals were assessed for diagnosis separately as qualitative data using appropriate logistic analysis. A separate analysis was performed to evaluate the impact of demographic information, the initial TLC, PS and IRIS scores on later diagnoses as indicated by SCID exams at follow up. Statistical tests were conducted 2 tailed, using an alpha value of .05. Multivariate analysis was performed to examine possible redundancies [21]. All analyses were done using the SPSS program (SPSS, Chicago, IL) [25].

**Results**

Of the 278 subjects enrolled, 266 (83%) completed at least one year of follow up. We subsequently re-interviewed 246 (77%) at two year and 224 (70%) at five year follow up. Post hoc analysis demonstrated that patients lost at the 1st, 2nd and 3rd follow up did not significantly differ from original enrollees in race, ethnicity, family history, education or initial PS, SCID or BPRS ratings. More males than females were lost to follow up (difference of 6%, 7% and 13% between genders for each wave of contact, respectively). The prognostic variables associated with conversion to psychosis were also examined by simple correlation, and subjected to multivariate analysis to remove redundancies among related measures. Several variables survived multivariate analysis to indicate significant risk for conversion. We found that conversion to psychosis in the first year was highly related to genetic risk for schizophrenia (chi Square = 9.68, p < .001), unusual thought content (chi square = 5.3, p < .01), ideas of reference (chi square =6.3, p < .01 and substance abuse (chi square 4.9, p < .01). Those who converted to psychosis tended to develop either schizophrenia (74%) or schizoaffective disorder (26%) by the end of year two according to our SCID results. Ideas of reference were a major feature in most of the individuals that converted, accounting for nearly all of the cases. Paranoia Scale items were very stable over the follow up visits for most patients, with 73% maintaining mild to moderate degrees of paranoid thinking in years one, two and five. Ideas of reference predicted conversion to psychosis ( chi square 5.2, p < .01), but did not predict later severity of deterioration. Only 15% were found to developed sophisticated paranoid delusions any of the three waves of interviews. While relatively rare in our sample, sophisticated paranoid delusions were negatively correlated with personality deterioration ( r = -.68, p < 001. ) and tended to be associated with good relatively higher levels of functioning at 5 years when compared to cases where paranoia did not persist. Multivariate analysis of all endorsed items on the combined rating scales found that ideas of reference had significant non-redundant predictive value for conversion to psychosis within two years (p < .001). Educational level, age of onset and handedness were not found to have predictive value in our population. Almost all conversions to psychosis had taken place by the second year of follow up for our study subjects. We found little progression towards new levels of psychosis between the second and third waves of evaluations. (See tables for data on years one, two and five). Over 90% of conversions had occurred by year two. We found that conversions during the period between years two and five were negligible. Patients who had sustained levels of paranoia at year five were more likely to be employed than non-paranoid subjects. They also maintained better BPRS scores at year five compared to disorganized subjects in spite of having chronic paranoia.

**Discussion**

Our findings indicate that early occurrence of ideas of reference is highly predictive of conversion to psychosis in a sample of young adults. This suggests that such ideation is important in the development of psychotic thinking. The timing of symptoms in our study agrees with the literature noting that most conversions to psychosis occurred in the first few years of illness. [7- 16, 22, 23, 24, 25, 26, 27]. As in previous studies we found high rates of conversion at the one year point (34%) with much lower rates at later contacts, 8.5% at two years and 1.5% at the five year point [5, 23, 24, 25, 26, 28,]. Our work suggests that the rate of conversion is highest in the first 2 years of the onset of symptoms and then rapidly tapers off [5, 23- 28]. The present study presents information on new measures at follow up in one, two and five years. We feel that the use of operational criteria enhanced predictive value in our study. Multivariate analysis found that ideas of reference ( the specific notion that others were discussing the individual in a negative way) strongly predicted conversion to psychosis at two years post onset, but did not predict future deterioration once psychosis was established. Analysis of data suggests that ideas of reference are common in young people who eventually become psychotic and that after two years of psychosis, but that sophisticated paranoid beliefs were associated with less deterioration according to employment demographics and the BPRS scale at year five.

Prediction algorithms which incorporate paranoia along with genetic risk, may have greater prognostic value than assessment of general symptoms alone. Social isolation has been associated with poor prognosis in previous studies [10, 26] and may be related to ideas of reference in some cases. The most sensitive indicator of conversion in our study appeared to be the notion that one was the subject of malicious conversation. This has been examined in the past, but seldom with operational criteria [1,6,13]. Within our sample, prodromal conversion to psychosis was associated with the persistent belief that one was the topic of persistent negative or malicious comments (in 78% of cases). This was found with both the PS and the IRIS. The more severe items of the PS were, however, associated with a psychosis of relatively good prognosis at year five compared to other cases that converted.

 The authors acknowledge potential problems in this or any long term prospective study. Our study population was relatively small limiting the analysis that might have been done in larger, more diverse sets of variables [ 29]. We also realize that any study using self-report of symptoms is open to errors from misreporting. Our subjects were people that were seeking

psychiatric treatment which could result in a selection bias. This group may not generalize to other young people with prodromal symptoms. We feel that the high rate of follow-up participation, use of reliable scales and good inter-rater reliability enhanced the integrity of the study.

We feel that the inclusion of operational criteria for ideas of reference allowed us to

predict conversion from prodroma to chronic psychosis with a high degree of sensitivity. The prediction of psychotic deterioration among subjects with high genetic loading is enhanced by inclusion of a detailed evaluation of paranoia. Studies that lacked detailed operational definitions may have been unable to capture data on the types of thought content and hence, be less accurate in making such predictions [26, 27, 28]. Based on our findings, it seems that certain kinds of delusions are more predictive than others for the conversion to psychosis in populations with positive genetic loading for schizophrenia. Once psychosis has developed the persistence of sophisticated forms of paranoid thinking were associated with better outcome over a period of five years based upon fewer hospitalizations, higher rates of employment and lower BPRS ratings when compared to other psychotic individuals in the study who demonstrated undifferentiated or disorganized symptoms. We encourage ongoing research on the effect of paranoia on prognosis.

**Tables**

 **for first year follow up**

Table 1. Demographic and symptomatic variables associated with conversion to psychosis at 1st year of follow up

By correlation coefficient post multivariate analysis, Not significant = NS

 Variable r significance

Level of education .09 p > .05 NS

Affective symptoms .04 p > .05 NS

Positive family history .32 p < .05

Unusual thoughts .65 p < .001

Paranoia .77 p < .001

Substance abuse .19 p < .05

Gender .08 p > .05 NS

Age onset .09 p > .05 NS

Hallucinations .18 p < .05

Table 2. Significant correlation of BPRS scores to original index factors in converters at 1 year

Variable r significance

Positive family history .17 p < .05

Unusual thoughts .61 p < .001

Paranoia .62 p < .001

Substance abuse .18 p < .05

Table 3. Overall regression analysis of significant predictive factors for conversion at 1 year

Variable F value significance

Substance abuse 3.84 p < .05

Positive family history 3.90 p < .05

Poverty of thought 7.77 p < .001

Ideas of reference 6.89 p < . 001

**Tables for second year follow up**

Table 4. Demographic and symptomatic variables associated with conversion to psychosis at 2nd year of follow up

By correlation coefficient post multivariate analysis, Not significant = NS

 Variable r significance

Level of education .09 p > .05 NS

Affective symptoms .04 p > .05 NS

Positive family history .22 p < .05

Unusual thoughts .62 p < .001

Paranoia .79 p < .001

Substance abuse .17 p < .05

Gender .08 p > .05 NS

Age onset .09 p > .05 NS

Hallucinations .19 p < .05

Table 5. Correlation of BPRS scores to original index factors in converters at 2 years

Variable r significance

Positive family history .20 p < .05

Unusual thoughts .68 p < .001

Paranoia .70 p < .001

Substance abuse .18 p < .05

Table 6. Overall regression analysis of significant predictive factors for conversion at 2 years

Variable F value significance

Substance abuse 3.45 p < .05

Positive family history 3.29 p < .05

Paranoia 7.30 p < .001

**References**

1. Bleuler, E. Dementia Praecox of the Group of Schizophrenias. New York, NY International Universities Press; 1911.
2. McGorry, P., Yung, A., Phillips, L. The “close-in” of ultra-high-risk model: a safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. **Schizophrenia Bulletin**, 1996; 22(2):771-790..
3. Yung, A., McGorry, P. the prodromal phase of first-episode psychosis: past and current conceptualizations. **Schizophrenia Bulletin**. 1996; 22(2):353-370.
4. Cannon, T., Clinical and genetic high-risk strategies in understanding vulnerability to psychosis. **Schizophrenia Research**. 2005; 79(1):35-44.
5. Cannon, T., Cadenhead, K., Cornblatt, B., Woods, S., Addington, J., Walker, E., Seldman, L., Perkins, D., Tsuang, M., McGlashan, Heinssen, R., Prediction of psychosis in youth at high clinical risk. **Archives of Clinical Psychiatry**. 2008; 65(1):28-35.
6. Kraepelin, E. Clinical Psychiatry: A textbook for students and physicians, 7th edition, New York, Macmillan, 1915
7. Ruhrman, S., Schultze-Lutter, F., Saloakngas, R., Heinman, M., Linszen, D., Dingemans, P., Birchwood, M., Patterson, P., Jucket, G., Heinz, A., Morrison, A., Lewis, S., Reventlow, H., Klosterkotter, J. Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. **Archives of Clinical Psychiatry**. 2010. 67(3); 241-51.
8. Cannon, T., Cornblatt, B., McGorry, P. the empirical status of the ultra-high-risk (prodromal) research paradigm. **Schizophrenia Bulletin**. 2007; 33(3):661-4.
9. Skalli, L., Nicole, L. Specialized first-episode psychosis services: a systematic review of the literature. **Encephale.** 2011. 37 Suppl 1:S66-76.
10. Wilcox, J., Winokur, G., Tsuang, M., Predictive value of thought disorder in new-onset

Psychosis, **Comprehensive Psychiatry** 2012, 53(6): 674-678**.**

1. Lenciu, M. Romosan, F., Bredicean, C., Romosan, R. First episode psychosis and treatment delay – causes and consequences. 2010. **Psychiatria Danubina** 22(4); 540-3.
2. Jaspers, K. Allgemeine psychopathologie. Berlin, Springer, 1913.
3. Cameron, N. The development of paranoid thinking. **Psychological Reviews.** 1943; 50, 219-233.
4. Freeman, D., Philippa, G., Bebbington, P., Smith, B., Rollison, R., Fowler, D., Kulpers, E., Katarzyna, R., Graham, D. Psychological investigation of the structure of paranoia in a non-clinical population **British Journal of Psychiatry**. 2005; 186:427-435
5. Spitznagel, M., Suhr, J. Neuropsychological impairment associated with symptoms of schizotypy: role of depressive and paranoid symptoms. **Journal of Nervous and Mental** **Disease**. 2004; 192(5):382-4.
6. Fernyhough, C., Jones, S., Whittle, C. Waterhouse, J., Bentall, R. Theory of mind, schizotypy, and persecutory ideation in young adults. **Cognitive Neuropsychiatry**. 2008; 13(3): 233-49.
7. Ryan A., Addington J, Bearden C., [Cadenhead,](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cadenhead%20KS%5BAuthor%5D&cauthor=true&cauthor_uid=29279247) K., [Cornblatt BA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cornblatt%20BA%5BAuthor%5D&cauthor=true&cauthor_uid=29279247), [Mathalon DH](https://www.ncbi.nlm.nih.gov/pubmed/?term=Mathalon%20DH%5BAuthor%5D&cauthor=true&cauthor_uid=29279247), [McGlashan TH](https://www.ncbi.nlm.nih.gov/pubmed/?term=McGlashan%20TH%5BAuthor%5D&cauthor=true&cauthor_uid=29279247), [Perkins DO](https://www.ncbi.nlm.nih.gov/pubmed/?term=Perkins%20DO%5BAuthor%5D&cauthor=true&cauthor_uid=29279247), [Seidman LJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Seidman%20LJ%5BAuthor%5D&cauthor=true&cauthor_uid=29279247), [Tsuang MT](https://www.ncbi.nlm.nih.gov/pubmed/?term=Tsuang%20MT%5BAuthor%5D&cauthor=true&cauthor_uid=29279247), [Woods SW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Woods%20SW%5BAuthor%5D&cauthor=true&cauthor_uid=29279247), [Cannon TD](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cannon%20TD%5BAuthor%5D&cauthor=true&cauthor_uid=29279247), [Walker EF](https://www.ncbi.nlm.nih.gov/pubmed/?term=Walker%20EF%5BAuthor%5D&cauthor=true&cauthor_uid=29279247)11 Latent class cluster analysis of symptom ratings identifies distinct subgroups within the clinical high risk for psychosis syndrome. **Schizophrenia** **Research** 2017; Dec 23. pii: S0920-9964(17)30753-3.
8. Fenigstein, A., Vanable, P. Paranoia and self-consciousness. **Journal of Personality and** **Social Psychology**. 1992; 62:129-138.
9. Overall, J., Gormann, D. The Brief Psychiatric Rating Scale. **Psychology Reports**. 1962; 10(2):799-812.
10. Spitzer, R., William, J., Gibbon, M., First, M., Structured Clinical Interview of DSM-III-R. Washington D.C., American Psychiatric Press, Inc. 1990.
11. Abraham, B. Ledolter, J. Statistical methods for forecasting. New York: Wiley & Sons. 2004.
12. Leversque, R., SPSS programming and data management: a guide of SPSS and SAS for users. 4th edition, Chicago: SPSS Inc. 2007.
13. Cornblatt, B., Lencz, T., Smith, C., Correll, C., Auther, A., Nakayama, E. the schizophrenia prodrome revisited: a Neurodevelopmental perspective. **Schizophrenia** **Bulletin** 2003; 29(4):633-651.
14. Cannon, T., Van Erp, T., Bearden, C., Loewy, R., Thompson, P. Toga, A., Huttunen, M., Keshavan, M., Seidman, L., Tsuang, M. Early and late Neurodevelopmental influences in the prodrome to schizophrenia: contributions of genes, environment and their interactions. **Schizophrenia Bulletin** 2003; 29(4):653-669.
15. Owens, D., Miller, P., Lawrie, S., Johnstone, E., Pathogenesis of schizophrenia: a psychopathological perspective. **British Journal of Psychiatry**. 2005; 185:386-393.
16. Yung, A., Stanford, C., Cosgrave, E. Killackey, E., Phillips, L., Nelson, B., McGorry, P. Testing the ultra high (prodromal) criteria for the prediction of psychosis in a clinical research sample of young people. **Schizophrenia Research.** 2006; 84(1):57-66.
17. Opjordsmoen, S., Retterstol, N. Dimensions of delusional experience and their value as predictors of long term outcome. **Psychopathology**. 2007; 40(5):278-81.
18. Helgason, L. Twenty year’s follow-up of first psychiatric presentation for schizophrenia: What could have been prevented? **Acta Psychiatrica Scandinavica**. 1990; 81:231-235.
19. Biau, D., Kerneis, S., Porcher, R. Statistics in Brief: The Importance of Sample Size in the Planning and Interpretation of Medical Research. **Clinical Therapeutics and Related** **Research**. 2008; 466:2282-2288.