Relationships of Age at Onset With Clinical Features and Cognitive Functions in a Sample of Schizophrenia Patients

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Background: A number of studies investigated the relationships of age at onset with clinical presentation and cognitive performance of schizophrenic patients. The aim of the present study was to assess demographic and clinical characteristics; psychopathologic, social functioning, and quality-of-life ratings; and neuropsychological measures in a sample of patients with stabilized schizophrenia and to identify which factors independently contributed to a multiple regression model with age at onset as the dependent variable.

Method: Ninety-six consecutive outpatients with schizophrenia (DSM-IV-TR criteria) were included in the study. Assessment instruments were as follows: a semistructured interview, the Clinical Global Impressions scale, the Comprehensive Psychopathological Rating Scale, and the Positive and Negative Syndrome Scale (PANSS) for psychopathology of schizophrenia; the Calgary Depression Scale for Schizophrenia (CDSS) for depression; the Social and Occupational Functioning Assessment Scale and the Sheehan Disability Scale for social functioning; the Quality of Life Scale; and a neuropsychological battery including the Wisconsin Card Sorting Test (WCST) and the Continuous Performance Test. Two models of multiple regression were tested: the first included clinical features and psychopathologic, social functioning, and quality-of-life scales; the second also considered neuropsychological variables. Data were collected from October 2001 to November 2002.

Results: The first multiple regression showed that age at onset was significantly related to scores on the PANSS subscale for negative symptoms ($p = .042$) and the CDSS ($p = .041$); the second regression found a relation of age at onset with PANSS score for negative symptoms ($p = .002$) and 2 neuropsychological measures, number of perseverative errors on the WCST and Continuous Performance Test reaction time ($p = .0005$ for both).

Conclusion: Our data indicate that, when results of neuropsychological tests are considered, early age at onset of schizophrenia is associated with severity of negative symptoms and compromised cognitive measures of executive functioning and sustained attention.

(J Clin Psychiatry 2004;65:908–914)

Received March 31, 2003; accepted Jan. 21, 2004. From the Unit of Psychiatry, Department of Neuroscience, University of Turin, Turin, Italy.

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Several studies have investigated which variables could be considered as predictors of the clinical features, the long-term outcome, and the treatment response of schizophrenia. Age at onset has been implicated as one potential prognostic determinant. A number of studies have reported statistically significant relationships between younger age at onset and a variety of demographic and clinical factors: male gender[1–4]; a higher level of familial loading for schizophrenia spectrum disorders[5]; a history of obstetric complications[6–8]; a higher rate of premorbid language and motor abnormalities[5,9]; a higher level of neuropathologic abnormalities[10]; an insidious and nonacute onset of symptoms, preceded by poor premorbid adjustment[11,12]; a longer duration of untreated prodromal psychotic symptoms[13]; and a poor response to neuroleptics.[12]

Many reports in the neuropsychological literature on schizophrenia have shown that patients with a younger age at onset are more likely to have impairment in cognitive performance (e.g., trails and card-sorting, abstraction and flexibility, semantic structure).[14–21]

An early onset of illness has been found to be a predictor of unfavorable prognosis, correlated to higher global severity[3]; to higher rates of chronicity, with at least some symptoms persisting between episodes[22–27]; and to a higher number of relapses.[28] Early-onset cases are believed to be considerably impeded in expected social development as early as the prodromal phase, because after onset of the first psychotic episode, very little improvement occurs in the patient's level of social adjustment.[2,3,24,25,29,30]

Still highly controversial are correlations between age at onset and psychopathologic factors. Some investigators observed a significant relationship between a younger age at onset and the presence of negative symptoms,[10,31] but other authors failed to find such evidence.[32–35] Some studies reported correlations between an early onset and a disorganization syndrome[35,36] or a combination of both nega-

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tive and disorganization symptoms.[37,38] Other authors correlated a congenital subtype of schizophrenia to the absence of affective symptoms.[14]

The purpose of the present study was to provide further data on the role of age at onset as a predictor of clinical and cognitive features in schizophrenia. Toward this aim, relations between age at onset and a series of demographic and clinical factors; psychopathologic, social functioning, and quality-of-life ratings; and neuropsychological measures were tested in a sample of stabilized schizophrenic patients.

METHOD

Patients

Ninety-six consecutive outpatients who were ≥ 18 years of age and had received a diagnosis of stabilized schizophrenia were included in this study. Data were collected from October 2001 to November 2002. Patients were referred to the Mental Health Department 1 South or the Center of Mental Health of Venaria (Turin, Italy) in the period between September 2001 and September 2002. The diagnosis of schizophrenia was made by 2 expert clinicians (P.R., S.B.) according to DSM-IV-TR[39] criteria and was confirmed using the Structured Clinical Interview for DSM-IV (SCID).[40] Schizophrenia was considered stabilized if patients' antipsychotic regimen had been unchanged for the last 6 months and they were judged clinically stable by the 2 clinicians.

Subjects were excluded if they had a current or past comorbid diagnosis of autistic disorder or another pervasive developmental disorder or bipolar disorder.

Each patient participated voluntarily in this study after providing written informed consent, and Declaration of Helsinki guidelines were followed. Patients were evaluated using a semistructured interview to assess demographic and clinical features. Data were collected to determine age, gender, education, age at onset of schizophrenia (operationalized in terms of first contact with a psychiatric service), duration of illness, duration of initially unmedicated psychosis (from first contact to first prescription of antipsychotic treatment), history of suicide attempts and self-mutilating behaviors, number of recurrences (readmissions to the hospital), occurrence of extrapyramidal symptoms (assessed according to administration of anticholinergic drugs), and occurrence of psychiatric disorders in first-degree relatives. All data were confirmed by clinical chart review.

Assessments

Axis I comorbidity was determined using the SCID. Assessment instruments chosen for this study were the Clinical Global Impressions scale (CGI),[41] the Comprehensive Psychopathological Rating Scale (CPRS),[42] the Positive and Negative Syndrome Scale (PANSS),[43] the Calgary Depression Scale for Schizophrenia (CDSS),[44] the Social and Occupational Functioning Assessment Scale (SOFAS),[45] the Sheehan Disability Scale,[46] and the Quality of Life Scale (QLS)[47] specifically designed for schizophrenic patients.

Patients were also assessed with a neuropsychological test battery including the vocabulary and block design subtests of the Wechsler Adult Intelligence Scale Revised (WAIS-R),[48] used as measures of verbal comprehension and perceptual organization; the Wechsler Memory Scale, third edition (WMS),[49] a measure of memory and learning abilities; the Wisconsin Card Sorting Test (WCST),[50] a widely used measure of abstract concept formation and ability to shift and maintain set; and the Continuous Performance Test (CPT),[51] a measure of capacity for sustained attention. Wisconsin Card Sorting Test performance is reported using the indices of number of categories completed and number and percentage of perseverative errors; CPT performance is reported according to the index of number of hits and the reaction time.

Prior to this study, interviewers received training sessions for the SCID and neuropsychological tests. The raters who administered the SCID, psychopathologic rating scales, and social functioning and quality-of-life scales were different from the psychologists who performed neuropsychological tests. These psychologists were unaware of patients' clinical characteristics and results on the psychiatric and functional rating scales.

Statistical Analysis

Statistical analysis was performed using the software system SPSS, version 11.0.1 (SPSS Inc., Chicago, Ill.).

General linear model (GLM) univariate analysis was performed to investigate the presence of significant relations between age at onset and any variable assessed in our patients: gender; education; duration of initially unmedicated psychosis; presence of suicide attempts; number of recurrences; administration of anticholinergic agents; Axis I comorbidity; family history of psychiatric disorders; scores on the CGI, CPRS, CDSS, SOFAS, Sheehan Disability Scale, QLS, WAIS-R vocabulary and block design, WMS, and PANSS positive symptoms, negative symptoms, and general psychopathology subscales; number of categories completed and number and percentage of perseverative errors on the WCST; and CPT number of hits and reaction time. To control for the effects of current age and duration of illness, these factors were included as covariates in the GLM analysis.

All variables significantly related to age at onset in GLM univariate analysis were subsequently analyzed using a stepwise multiple regression to assess their independent contribution to age at onset. Two models were tested, both using age at onset as the dependent variable: in the first model, only demographic and clinical factors and rating scale scores were considered; in the second anal-

Table 1. Age at Onset of Illness According to Categorical Variables and GLM Univariate Analysis With Current Age and Duration of Illness as Covariates

Variable	N	%	Age at Onset Mean	SD	F	p
Gender						
Female	39	40.6	26.21	6.77	1.512	.222
Male	57	59.4	24.21	5.64		
Suicide attempts						
Yes	18	18.7	24.13	4.60	0.104	.748
No	78	81.3	25.21	6.45		
Anticholinergic drugs						
Yes	21	21.9	20.7	5.23	0.082	.775
No	75	78.1	26.2	5.90		
Axis I comorbidity						
Yes	49	51	24.38	5.19	2.007	.160
No	47	49	25.70	7.03		
Family history of psychiatric disorders						
Yes	35	36.5	25.94	5.46	2.229	.139
No	61	63.5	24.50	6.51		
Type of schizophrenia						
Paranoid	56	58.3	28.50	5.27	0.003	.954
Nonparanoid	40	41.7	19.89	2.99		

Abbreviation: GLM = general linear model.

Table 2. Continuous Clinical Variables and GLM Univariate Analysis With Current Age and Duration of Illness as Covariates

Variable	Mean	SD	F	p
Education, y	10.47	3.10	0.840	.558
Duration of unmedicated psychosis, mo	10.95	18.48	0.820	.620
No. of recurrences	4.02	5.00	0.539	.871
CDSS score	4.37	3.62	3.456	.001
PANSS score				
Positive	13.74	6.94	1.545	.103
Negative	17.85	9.61	2.182	.008
General psychopathology	33.66	11.78	2.001	.011
CPRS score	28.39	16.22	2.351	.003
CGI score	3.83	1.15	1.412	.220
SOFAS score	55.83	15.29	4.708	.0005
QLS score	74.04	23.62	1.454	.105
Sheehan Disability Scale score	4.77	3.13	2.605	.001

Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia, CGI = Clinical Global Impressions scale, CPRS = Comprehensive Psychopathological Rating Scale, GLM = general linear model, PANSS = Positive and Negative Syndrome Scale, QLS = Quality of Life Scale, SOFAS = Social and Occupational Functioning Assessment Scale.

Table 3. Continuous Neuropsychological Variables and Results of GLM Univariate Analysis With Current Age and Duration of Illness as Covariates

Variable	Mean	SD	F	p
WAIS-R				
Vocabulary	7.74	2.13	1.977	.062
Block design	7.52	2.62	2.616	.019
Wechsler Memory Scale	86.91	14.50	3.340	.0005
WCST				
No. of categories	3.66	2.27	0.921	.487
No. of perseverative errors	30.61	23.24	6.452	.0005
% of perseverative errors	57.15	36.65	0.751	.788
CPT				
No. of hits	15.69	6.03	0.588	.860
Reaction time, ms	575.78	237.78	14.206	.0005

Abbreviations: CPT = Continuous Performance Test, GLM = general linear model, WAIS-R = Wechsler Adult Intelligence Scale Revised, WCST = Wisconsin Card Sorting Test.

ysis, neuropsychological test scores were also included. The probability used for entry and removal variables from stepwise regression was 0.05 and 0.10.

To assess the effects of negative symptoms not influenced by depression, statistical analysis was repeated after removing patients who met criteria for depression based on the CDSS (i.e., a score of 6 or above).

RESULTS

Patients in our sample had a mean ± SD age of 35.10 ± 10.12 years; there were 39 women (40.6%) and 57 men (59.4%). Mean age at onset of schizophrenia was 25.02 ± 6.17 years; duration of illness was 10.43 ± 8.94 years.

Relations of Age at Onset With Clinical Factors and Rating Scales

Results of GLM univariate analysis for categorical and continuous clinical factors and rating scales are summarized in Tables 1 and 2. No significant relation with age at onset was found for demographic or clinical factors. When rating scale scores were considered, a significant relation was found for the CPRS (p = .003), PANSS subscales for negative symptoms (p = .008) and general psychopathology (p = .011), CDSS (p = .001), SOFAS (p = .0005), and Sheehan Disability Scale (p = .001).

Relations of Age at Onset With Neuropsychological Data

Results of GLM univariate analysis for neuropsychological measures are reported in Table 3. Relations with age at onset were significant for the following measures: WMS score (p = .0005), WCST number of perseverative errors (p = .0005), and CPT reaction time (p = .0005).

Multiple Regression Analysis

The results of multiple regression analysis that included rating scale scores showed that 2 variables were significantly related to age at onset in our sample of schizophrenia patients: CDSS score and PANSS score for negative symptoms both had a negative relation (p = .041 and .042, respectively) (Table 4). This model explained 15.2% of the variance in age at onset. When neuropsychological test scores were also included in the regression model, the variables significantly related to age at onset of schizophrenia were PANSS negative symptoms subscale score (p = .002), WCST number of perseverative errors (p = .0005), and CPT reaction time (p = .0005) (Table 5); all coefficients were negative. The second model accounted for 56.7% of variance.

Table 4. First Model of Stepwise Multiple Regression: Contribution of Rating Scale Scores to Age at Onset[a]

Variable	B	SE	β	t	p
Constant	29.148	1.278		22.803	.0005
CDSS score	–0.393	0.189	–0.230	–2.075	.041
PANSS negative symptoms score	–0.146	0.071	–0.228	–2.064	.042

[a]Rating scales found to be significantly related to age at onset using GLM univariate analysis were included in the model.
Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia, GLM = general linear model, PANSS = Positive and Negative Syndrome Scale.

Table 5. Second Model of Stepwise Multiple Regression: Contribution of Both Rating Scale Scores and Neuropsychological Measures to Age at Onset[a]

Variable	B	SE	β	t	p
Constant	17.409	2.197		7.923	.0005
CPT reaction time	–0.012	0.002	–0.475	–4.842	.0005
WCST no. of perseverative errors	–0.102	0.025	–0.383	–4.075	.0005
PANSS negative symptoms score	–0.195	0.059	–0.325	–3.299	.002

[a]Rating scales and neuropsychological measures found to be significantly related to age at onset using GLM univariate analysis were included in the model.
Abbreviations: CPT = Continuous Performance Test, GLM = general linear model, PANSS = Positive and Negative Syndrome Scale, WCST = Wisconsin Card Sorting Test.

Analysis of Data of Nondepressed Patients

After exclusion of patients with a CDSS score of ≥ 6, the same statistical procedures were performed in the 66 remaining patients. When only clinical variables were considered, the results of multiple regression showed that age at onset was significantly related to a single factor: PANSS negative symptoms subscale score ($p = .001$). This factor accounted for 14.8% of variance. When neuropsychological variables were also included, the results of multiple regression indicated that age at onset was related to the same 3 factors as in the total group: PANSS negative symptoms subscale score ($p = .003$), WCST number of perseverative errors ($p = .002$), and CPT reaction time ($p = .0005$); all coefficients were negative. The model explained 64.8% of the variance in age at onset.

DISCUSSION

The present study was performed to test the relationships of age at onset with clinical characteristics and cognitive functions of schizophrenic patients by using multiple regression analysis. As patients with an early onset of illness are likely to be younger and to have been ill longer than those with a later onset, analysis of data was performed controlling for current age and duration of illness. Although a series of factors was found to be related to age at onset when GLM analysis was performed, only a few of them were independently related to age at onset in the results of multiple regression; our discussion section focuses mainly on these factors.

Age at onset in our study was slightly higher than is generally reported in populations of schizophrenic patients, particularly when assessed at first psychotic episode.[13,36,52] A possible explanation is that a high proportion of our patients (about 60%) present the paranoid type of schizophrenia, which is characterized by considerably higher age at onset (mean age of 28.5 years vs. 19.9 years in patients with nonparanoid schizophrenia). An unusual characteristic of our sample is the lack of difference in age at onset between men and women, as later age at onset is usually reported for females.[36,53,54]

Considering the results of GLM univariate analysis, it is surprising that education was not related to age at onset, as patients should have a lower educational level if illness onset occurs when they are still attending school. A likely explanation is that most of our patients with later age at onset had a poor education, perhaps due to low socioeconomic status. Unfortunately, data concerning social indicators were not collected in our sample.

Two regression models were tested with age at onset as the dependent variable. The first model considered demographic and clinical factors and psychiatric and functional rating scales that were found to be significantly related to age at onset using GLM univariate analysis. We found that both negative and depressive symptoms, rated with the PANSS and CDSS, were inversely related to age at onset in this sample of stabilized schizophrenia patients: patients with lower age at onset had higher severity of negative and depressive symptoms. The findings on negative symptoms are consistent with data provided by several authors[10,17,19,31,55] who observed a significant association between negative symptoms and earlier onset of schizophrenic illness, although discordant evidence was also reported in the literature.[33–35]

Our finding concerning a relation between severity of depressive symptoms and earlier age at onset may be difficult to compare with other studies, as this association has rarely been investigated. Only Murray et al.,[14] after dividing patients with schizophrenia into congenital and adult-onset subtypes, listed typical absence of affective symptoms among the distinctive features of the first group. This report seems to contrast with our data, although our patients with an earlier onset are not comparable with the clinical subtype proposed by Murray et al. Further investigations are clearly required to define the association between depression and early age at onset.

A possible explanation of the partial discordance of results among studies concerns heterogeneity of selection criteria, methods, and assessment instruments. Analysis of the available data raises the question of whether a distinction between negative and depressive symptoms can be reliably made when characterizing clinical features of schizophrenic patients. Indeed, several authors indicated

the extensive overlapping of negative and depressive syndromes in a number of important respects, such as poverty of thought and speech, blunted affect, decreased motor activity, apathy and avolition, and social withdrawal.[56–60] However, other authors supported the hypothesis that negative and depressive symptoms can be conceptualized as 2 separate syndromes that can coexist in schizophrenic illness.[61–64]

To address this controversial issue, we chose to rate depression in our sample of schizophrenia patients by administering the CDSS, a standardized instrument specifically designed to allow the identification of depressive symptoms and their distinction from the negative syndrome.[65–68] As we found that negative and depressive symptom clusters independently contributed to the regression model, our data suggest that these factors represent 2 distinct psychopathologic dimensions and should be separately assessed and treated in patients with schizophrenia. This conclusion is further confirmed by the analysis of data performed after removing depressed patients from the analysis: in the subgroup of patients who still had negative symptoms not explained by depression, multiple regression showed that PANSS negative symptoms subscale score was the only clinical factor significantly related to age at onset.

The interest in identifying and reliably discriminating these 2 symptom clusters is increased by the fact that available drug treatments for schizophrenia have not definitively proved their efficacy for either negative or depressive symptoms.[69] In fact, negative symptoms of schizophrenia are expected to respond to antipsychotic therapy less robustly than positive symptoms do.[36] Although the efficacy of atypical antipsychotic medications in treating negative symptoms has usually been found superior to that of conventional neuroleptics, the amount of clinical improvement with a particular agent across different studies has had considerable variation.[70] Additionally, it remains unclear whether these agents treat core negative symptoms of schizophrenia or simply induce less secondary psychopathology.[71]

As for depressive symptoms, appropriate treatment strategies in schizophrenic patients are currently being defined. Various therapeutic options have been proposed, including conventional and atypical antipsychotic agents and combination with antidepressant medications, but little agreement exists among clinicians on the real efficacy of these interventions.[59,64,72–76]

In the second regression model of our study, neuropsychological measures that were found to be significantly related to age at onset by GLM analysis were added to factors considered in the first model. Results of this regression analysis showed that 2 neuropsychological variables, WCST number of perseverative errors and CPT reaction time, together with the PANSS measure of negative symptoms, contributed independently to the model. Together, the 3 factors accounted for a high percentage of variance in age at onset, over 55%. These data are consistent with the results of previous studies suggesting an association of younger age at onset with impairment of cognitive performance.[14–21] There is abundant evidence that neuropsychological dysfunction is a core feature of schizophrenic illness and that it reflects the underlying pathophysiologic process, which is believed to be more severe in earlier onset patients.[5,10,77] It is notable that negative symptoms represent the only psychopathologic factor that still contributed to age at onset when neuropsychological variables were also included in the multiple regression, suggesting a strong association of these 2 clinical features in schizophrenia patients and encouraging further studies on this specific issue.

A methodological limit of our study should be mentioned. Age at onset has been established using retrospective methods and based on anamnestic data and clinical chart review. It is difficult to pinpoint the exact age at onset, since some patients remain at home unmedicated for years, and others, because of accidents of social setting, may come to medical attention early. Early psychotic symptoms are sometimes subtle or benign in content and go without treatment, which creates an opportunity for type II statistical error. However, a prospective follow-up study assessing age at onset in schizophrenia with reliable criteria would be difficult to perform: it would require a large cohort of children and adolescents to be evaluated and regularly followed for a long time period. Perhaps a more reliable assessment of age at onset could be performed in a sample of patients with a shorter duration of illness, the onset being more recent and more easily recalled by patients.

Another limitation of the study is that patients' social functioning and quality of life were not reassessed after a consistent period of standard clinical management in order to obtain reliable information on effects of age at onset on functional outcome of schizophrenia.

In conclusion, we found that earlier age at onset of schizophrenia is associated with a more severe form of the illness, with greater negative symptoms and neurocognitive deficits in executive functioning and sustained attention. Statistical analysis demonstrated that these relationships were not accounted for by the duration of illness. However, we should avoid excessive stigmatization of early-onset psychosis patients given that conclusive data on the prognosis of their conditions are not available.

REFERENCES

1. Castle DJ, Murray RM. The epidemiology of late-onset schizophrenia. Schizophr Bull 1993;19:691–700
2. Ganev K. Long-term trends of symptoms and disability in schizophrenia and related disorders. Soc Psychiatry Psychiatr Epidemiol 2000;35: 389–395
3. Häfner H. Onset and early course as determinants of the further course of schizophrenia. Acta Psychiatr Scand 2000;102:44–48

4. Moriarty PJ, Lieber D, Bennett A, et al. Gender differences in poor outcome patients with lifelong schizophrenia. Schizophr Bull 2001; 27:103–113
5. Nicolson R, Rapoport JL. Childhood-onset schizophrenia: rare but worth studying. Biol Psychiatry 1999;46:1418–1428
6. O'Callaghan E, Gibson T, Colohan HA, et al. Risk of schizophrenia in adults born after obstetric complications and their associations with early onset of illness: a controlled study. BMJ 1992;305:1256–1259
7. Verdoux H, Geddes JR, Takei N, et al. Obstetric complications and age at onset in schizophrenia: an international collaborative meta-analysis of individual patient data. Am J Psychiatry 1997;154:1220–1227
8. Rosso IM, Cannon TD, Huttunen T, et al. Obstetric risk factors for early-onset schizophrenia in a Finnish birth cohort. Am J Psychiatry 2000;157:801–807
9. Hollis C. Child and adolescent (juvenile onset) schizophrenia: a case-control study of premorbid developmental impairments. Br J Psychiatry 1995;166:489–495
10. Corrigal RJ, Murray RM. Twin concordance for congenital and adult-onset psychosis: a preliminary study of the validity of a novel classification of schizophrenia. Acta Psychiatr Scand 1994;89:142–145
11. Ciompi L. Learning from outcome studies: toward a comprehensive biological-psychosocial understanding of schizophrenia. Schizophr Res 1988;1:373–384
12. Roy MA, Mérette C, Maziade M. Subtyping schizophrenia according to outcome or severity: a search for homogeneous subgroups. Schizophr Bull 2001;27:115–138
13. Ho BC, Andreasen NC, Flaum M, et al. Untreated initial psychosis: its relation to quality of life and symptom remission in first episode schizophrenia. Am J Psychiatry 2000;157:808–815
14. Murray RM, Castle D, O'Callaghan E, et al. The neurodevelopmental and adult schizophrenias: Kraepelin lost and Kraepelin found. Schizophr Res 1991;4:282–283
15. Paulsen JS, Heaton RK, Sadek JR, et al. The nature of learning and memory impairments in schizophrenia. J Int Neuropsychol Soc 1995; 1:88–99
16. Paulsen JS, Romero R, Chan A, et al. Impairment of the semantic network in schizophrenia. Psychiatry Res 1996;63:109–121
17. Hoff AL, Harris D, Faustman WO, et al. A neuropsychological study of early onset schizophrenia. Schizophr Res 1996;20:21–28
18. Jacobsen LK, Rapaport JL. Childhood-onset schizophrenia: implications of clinical and neurobiological research. J Child Psychol Psychiatry 1998;39:101–113
19. Jeste DV, McAdams LA, Palmer BW, et al. Relationship of neuropsychological and MRI measures to age of onset of schizophrenia. Acta Psychiatr Scand 1998;98:156–164
20. Bender S, Müller B, Oades RD, et al. Conditioned blocking and schizophrenia: a replication and study of the role of symptoms, age, onset-age of psychosis and illness-duration. Schizophr Res 2001;49: 157–170
21. Sumiyoshi C, Matsui M, Sumiyoshi T, et al. Semantic structure in schizophrenia as assessed by the category fluency test: effect of verbal intelligence and age of onset. Psychiatry Res 2001;105:187–199
22. Werry JS, McClellan JM, Chard L. Early-onset schizophrenia, bipolar and schizoaffective disorders: a clinical follow-up study. J Am Acad Child Adolesc Psychiatry 1991;30:457–465
23. McClellan JM, Werry JS, Ham M. A follow-up study of early onset psychosis: comparison between outcome diagnoses of schizophrenia, mood disorders, and personality disorders. J Autism Dev Disord 1993; 23:243–262
24. Maziade M, Gingras N, Bouchard S, et al. Long-term stability of diagnosis and symptom dimensions in a systematic sample of patients with onset of schizophrenia in childhood and early adolescence, 1: nosology, sex and age of onset. Br J Psychiatry 1996;169:361–370
25. Maziade M, Bouchard S, Gingras N, et al. Long-term stability of diagnosis and symptom dimensions in a systematic sample of patients with onset of schizophrenia in childhood and early adolescence, 2: positive/negative distinction and childhood predictors of adult outcome. Br J Psychiatry 1996;169:371–378
26. Eggers C, Bunk D. The long-term course of early-onset schizophrenia. Schizophr Bull 1997;23:105–118
27. Meltzer HY, Rabinowitz J, Lee MA, et al. Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance. Am J Psychiatry 1997;154:475–482
28. Altamura AC, Bassetti R, Sassella F, et al. Duration of untreated psychosis as a predictor of outcome in first-episode schizophrenia: a retrospective study. Schizophr Res 2001;52:29–36
29. Gillberg IC, Hellgren L, Gillberg C. Psychotic disorders diagnosed in adolescence: outcome at age 30 years. J Child Psychol Psychiatry 1993;34:1173–1185
30. Lay B, Blanz B, Hartmann M, et al. The psychosocial outcome of adolescent-onset schizophrenia: a 12-year follow-up. Schizophr Bull 2000;26:801–816
31. Mayerhoff DI, Loebel AD, Alvir JM, et al. The deficit state in first-episode schizophrenia. Am J Psychiatry 1994;151:1417–1422
32. Carpenter WT, Heinrichs DW, Wagman AM. Deficit and nondeficit forms of schizophrenia: the concept. Am J Psychiatry 1988;145:578–583
33. Kirkpatrick B, Ram R, Bromet E. The deficit syndrome in the Suffolk County Mental Health Project. Schizophr Res 1996;22:119–126
34. Buchanan RW, Strauss ME, Breier A, et al. Attentional impairments in deficit and nondeficit forms of schizophrenia. Am J Psychiatry 1997;154:363–370
35. Kirkpatrick B, Castle D, Murray R, et al. Risk factors for the deficit syndrome of schizophrenia. Schizophr Bull 2000;26:233–242
36. Malla AK, Norman RMG, Manchanda R, et al. One year outcome in first episode psychosis: influence of DUP and other predictors. Schizophr Res 2002;54:231–242
37. Castle DJ, Sham PC, Wessely S, et al. The subtyping of schizophrenia in men and women: a latent class analysis. Psychol Med 1994;24:41–51
38. Sham PC, Castle DJ, Wessely S, et al. Further exploration of a latent class typology of schizophrenia. Schizophr Res 1996;20:105–115
39. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Press; 2000
40. First MB, Gibbon M, Spitzer RL, et al. Structured Clinical Interview for DSM-IV Disorders (SCID). Washington, DC: American Psychiatric Press; 1997
41. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
42. Asberg M, Montgomery SA, Perris C, et al. Comprehensive Psychopathological Rating Scale. Acta Psychiatr Scand 1978;271:5–27
43. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
44. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. Schizophr Res 1990;3:247–251
45. Goldman HH, Skodol AE, Lave TR. Revising Axis V for DSM-IV: a review of measures of social functioning. Am J Psychiatry 1992; 149:1148–1156
46. Sheehan DV, Harnett Sheehan K, Ray BA. The measurement of disability. Int Clin Psychopharmacol 1996;11:89–95
47. Heinrichs DW, Hanion TE, Carpenter WT. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr Bull 1984;3:388–398
48. Wechsler D. WAIS-R Manual. 3rd ed. New York, NY: Psychological Corporation; 1997
49. Wechsler D. Wechsler Memory Scale. 3rd ed. New York, NY: Psychological Corporation; 1997
50. Heaton RK. Wisconsin Card Sorting Test Manual. Odessa, Fla: Psychological Assessment Resources; 1981
51. Cornblatt B, Keilp J. Impaired attention, genetics and psychophysiology of schizophrenia. Schizophr Bull 1994;20:31–46
52. Malla AK, Takhar JJ, Norman RMG, et al. Negative symptoms in first episode non-affective psychosis. Acta Psychiatr Scand 2002;105: 431–439
53. Riecher-Rossler A, Häfner H. Gender aspects in schizophrenia: bridging the border between social and biological psychiatry. Acta Psychiatr Scand 2000;102(suppl 407):58–62
54. Usall J, Araya S, Ochoa S, et al. Gender differences in a sample of schizophrenic outpatients. Compr Psychiatry 2001;42:301–305
55. Guerra A, Fearon P, Sham P, et al. The relationship between predisposing factors, premorbid function and symptom dimensions in psychosis: an integrated approach. Eur Psychiatry 2002;17:311–320
56. Andreasen NC. Negative symptoms in schizophrenia. Arch Gen Psychiatry 1982;39:784–788
57. Carpenter WT, Heinrichs DW, Alphs LD. Treatment of negative symptoms. Schizophr Bull 1985;11:440–452

58. Siris SG, Adan F, Cohen M, et al. Post psychotic depression and negative symptoms: an investigation of syndromal overlap. Am J Psychiatry 1988;145:1532–1537
59. Siris SG. Depression in schizophrenia: perspective in the era of "atypical" antipsychotic agents. Am J Psychiatry 2000;157:1379–1389
60. Hausmann A, Fleischhacker WW. Differential diagnosis of depressed mood in patients with schizophrenia: a diagnostic algorithm based on a review. Acta Psychiatr Scand 2002;106:83–96
61. Newcomer JW, Faustman WO, Heh W, et al. Distinguishing depression and negative symptoms in unmedicated patients with schizophrenia. Psychiatry Res 1990;31:243–250
62. Goldman RS, Tandon R, Liberzon I, et al. Measurement of depression and negative symptoms in schizophrenia. Psychopathology 1992;25: 49–56
63. Kibel DA, Laffont I, Liddle PF. The composition of the negative syndrome of chronic schizophrenia. Br J Psychiatry 1993;162:744–750
64. Tapp A, Kilzieh N, Wood AE, et al. Depression in patients with schizophrenia during an acute psychotic episode. Compr Psychiatry 2001;42:314–318
65. Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. Br J Psychiatry 1993;163:39–44
66. Addington D, Addington J, Maticka-Tyndale E. Specificity of the Calgary Depression Scale for schizophrenics. Schizophr Res 1994;11:239–244
67. Bernard D, Lançon C, Auquier P, et al. Calgary Depression Scale for Schizophrenia: a study of the validity of a French-language version in a population of schizophrenic patients. Acta Psychiatr Scand 1998;97:36–41
68. Lançon C, Auquier P, Reine G, et al. Relationship between depression and psychotic symptoms of schizophrenia during an acute episode and stable period. Schizophr Res 2001;47:135–140
69. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Schizophrenia. Am J Psychiatry 1997;154(suppl 4):1–63
70. Tandon R, Jibson MD. Efficacy of newer generation antipsychotics in the treatment of schizophrenia. Psychoneuroendocrinology 2003;1:9–26
71. Javitt DC. Management of negative symptoms of schizophrenia. Curr Psychiatry Rep 2001;3:413–417
72. Krakowski M, Czobor P, Volakva J. Effect of neuroleptic treatment on depressive symptoms in acute schizophrenia episodes. Psychiatry Res 1997;71:19–26
73. Levinson DF, Umapathy C, Musthaq M. Treatment of schizoaffective disorder and schizophrenia with mood symptoms. Am J Psychiatry 1999;156:1138–1148
74. Hausmann A, Fleischhacker WW. Depression in patients with schizophrenia: prevalence and diagnostic and treatment considerations. CNS Drugs 2000;14:289–299
75. Addington D, Azorin JM, Falloon IRH, et al. Clinical issues related to depression in schizophrenia: an international survey of psychiatrists. Acta Psychiatr Scand 2002;105:189–195
76. Whitehead C, Moss S, Cardno A, et al. Antidepressants for people with both schizophrenia and depression. Cochrane Database Syst Rev 2002;2:CD002305
77. Weinberger DR, Egan MF, Bertolino A, et al. Prefrontal neurons and the genetics of schizophrenia. Biol Psychiatry 2001;50:825–844

