Remission in First-Episode Psychosis: Predictor Variables and Symptom Improvement Patterns

Robin Emsley, M.D.; Piet P. Oosthuizen, M.D.; Martin Kidd, Ph.D.; Liezl Koen, M.B.; Dana J. H. Niehaus, M.D.; and H. Jadri Turner, M.B.

Background: Previous attempts to identify clinically useful predictors of treatment outcome in schizophrenia have been hampered by methodological inconsistencies, including a lack of standardized outcome measures. Recently proposed operationally defined criteria for remission provide an opportunity to readdress this topic.

Method: We applied the remission criteria to a sample of 57 subjects with first-episode psychosis (DSM-IV schizophrenia, schizoaffective disorder, or schizophreniform disorder), treated according to a fixed protocol in a prospective study. Subjects were recruited between April 1999 and January 2000 and were followed for 2 years. Various demographic, baseline clinical, and early-response variables were subjected to discriminant analysis for their ability to predict remission or nonremission. We also assessed the symptom improvement patterns over time and compared endpoint psychopathology in the remitters and nonremitters.

Results: A model incorporating neurologic soft signs, 6-week treatment response, duration of untreated psychosis, marital status, and Positive and Negative Syndrome Scale excited factor baseline score was able to correctly predict 89% of the remitters and 86% of the nonremitters. Symptom reduction at 6 weeks, including core psychotic symptoms, was significant in both groups (remitters, $p < .0001$; nonremitters, $p < .0001$), although reduction was substantially greater in the remission group ($p = .004$). Thereafter, the remission group continued to improve ($p < .01$), while the nonremitting group failed to do so ($p = .55$). Considerable overlap of endpoint symptoms was observed, and depressive symptom scores were similar in remitters and nonremitters.

Conclusion: A combination of demographic, baseline clinical, and acute treatment response variables may accurately predict treatment outcome. Persistent noncore psychotic symptoms in subjects meeting proposed remission criteria require further investigation.

(J Clin Psychiatry 2006;67:1707–1712)

Received Nov. 16, 2005; accepted May 24, 2006. From the Department of Psychiatry, Faculty of Health Sciences (Drs. Emsley, Oosthuizen, Koen, Niehaus, and Turner), and the Department of Statistics and Actuarial Science (Dr. Kidd), University of Stellenbosch, Cape Town, South Africa.

Supported in part by the Medical Research Council of South Africa.

Dr. Emsley has received grant/research support from Janssen and has served on speakers/advisory boards for and received honoraria from AstraZeneca, Bristol-Myers Squibb, Janssen, Lundbeck, Organon, Pfizer, and Servier. Dr. Oosthuizen has served on speakers/advisory boards for and received honoraria from AstraZeneca, Eli Lilly, Janssen, Lundbeck, and Pfizer. Drs. Kidd, Koen, Niehaus, and Turner report no additional financial affiliations or other relationships relevant to the subject of this article.

Corresponding author and reprints: Robin Emsley, M.D., Department of Psychiatry, University of Stellenbosch, P.O. Box 19063, Tygerberg 7505, Cape Town, South Africa (e-mail: rae@gerga.sun.ac.za).

Since the introduction of antipsychotic medication some 50 years ago, considerable attempts have been made to identify predictors of treatment outcome.[1] Reliable predictors of antipsychotic treatment outcome would be of great benefit, particularly by avoiding unnecessary persistence with ineffectual treatment before attempting alternative strategies. This in turn would reduce the development of side effects, the risk of accruing morbidity, the duration of hospitalization, the level of care required, the amounts of concomitant medication prescribed, and overall costs incurred.

Factors determining the response to antipsychotic treatment in schizophrenia are poorly understood, and results of studies thus far have been inconclusive and sometimes conflicting.[2] A poorer response has been associated, amongst other factors, with male gender, history of obstetric complications, more severe positive symptoms, the development of parkinsonism during antipsychotic treatment,[3] extrapyramidal symptoms prior to antipsychotic exposure,[4] neurologic soft signs,[5] the development of tardive dyskinesia, family history of schizophrenia,[6] and prolonged duration of untreated psychosis (DUP).[7] However, associations as such do not necessarily imply predictive value, and none of these factors can be regarded as clinically useful in forecasting treatment outcome.[2] An alternative approach has recently produced promising results: early treatment response appears to closely parallel later outcome,[8,9] and recent evidence has emerged that a lack of early-treatment symptom reduction may be an accurate predictor of later nonresponse.[2]

Part of the difficulty in interpreting the findings of studies to date is related to the divergent methodologies that were employed.[10] Sample populations (e.g., first-episode, multi-episode), treatment durations, and assessment instruments differ across studies. Another significant problem has been that the endpoint measures of outcome have varied widely. For example, clinical treatment trials often report a reduction in symptom severity from baseline to endpoint as the primary outcome measure, while other studies have attempted to define criteria for treatment response (e.g., 20% improvement in psychopathology scores),[11] relapse,[12] or remission.[13] Recently, in the hope of improving the assessment of treatment outcome, operational criteria defining remission in schizophrenia were proposed by a "Remission in Schizophrenia Working Group."[14] These criteria define remission according to a threshold of severity of selected rating scale items rather than percentage improvements from a particular baseline. The items were selected on the basis of their representing 3 major symptom domains identified in factor analyses (negative, psychosis, and disorganized factors) and the 5 criteria specified in DSM-IV for a diagnosis of schizophrenia. The proposed criteria define remission as absent, borderline, or mild symptom intensity level, at which such symptoms do not influence an individual's behavior. An additional requirement is that these criteria must have been met for a duration of at least 6 months.[14]

We applied these criteria in a post hoc fashion to a sample of subjects with first-episode psychosis who were treated according to a fixed protocol over 24 months, and we evaluated various potential predictors of outcome. The primary aim of our study was to identify any baseline and early-treatment variables that could be useful to clinicians in predicting remission and nonremission. As a secondary aim, we explored the symptom improvement patterns over time and differences in endpoint psychopathology in remitters and nonremitters.

METHOD

Subjects

The sample comprised 57 participants recruited between April 1999 and January 2000 and followed in a 2-year prospective study of first-episode psychosis in the Stikland Hospital catchment area in Cape Town, South Africa. The patient sample and study procedure have been described in detail elsewhere.[15] Briefly, inclusion criteria comprised inpatients or outpatients aged 16 to 55 years meeting DSM-IV[16] diagnostic criteria for schizophreniform disorder, schizophrenia, or schizoaffective disorder and who had been exposed to less than 4 weeks of antipsychotic treatment. Exclusion criteria were another DSM-IV Axis I diagnosis including substance abuse or dependence, significant general medical condition, and mental retardation. The study was approved by the ethics committee of the University of Stellenbosch, and subjects and/or their guardians provided written informed consent to participate in the trial.

Assessments

Participants were assessed by means of the Structured Clinical Interview for DSM-IV.[17] Psychopathology was measured by means of the Positive and Negative Syndrome Scale (PANSS)[18] and the Calgary Depression Scale for Schizophrenia,[19] and extrapyramidal symptoms were measured by means of the Abnormal Involuntary Movement Scale,[20] the Barnes Akathisia Scale,[21] and the Simpson-Angus Scale.[22] For the purpose of this analysis we used baseline, 6- and 12-week, and then 3-month assessments.

Treatment

Subjects were treated with low doses of haloperidol according to a fixed protocol starting at 1 mg/day, gradually increasing the dose for nonresponders (≤ 20% reduction in PANSS total score) to a maximum of 10 mg/day. The treatment was generally effective and well tolerated.[15]

Remission Criteria

The symptom severity threshold comprises a score of 3 (mild) or less on each of the following PANSS items: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), blunted affect (N1), social withdrawal (N4), lack of spontaneity (N6), mannerisms/posturing (G5), and unusual thought content (G9). The minimum time threshold for maintaining these symptom severity levels is 6 months.[14]

Symptom Improvement Patterns

Positive and Negative Syndrome Scale total scores over time were compared between remitters and nonremitters by repeated-measures analysis of variance. To examine whether any initial symptom reduction in the nonremitting group could be accounted for by improvement in noncore psychotic symptoms, we compared baseline with week 6 reductions in the PANSS symptoms used to define remission.[14] Endpoints for PANSS total and factor scores, as well as the Calgary Depression Scale for Schizophrenia scores, were compared between the 2 groups.

Predictors of Remission

The following variables were investigated as potential predictors of remission: sex, age, diagnosis (schizophrenia vs. schizophreniform/schizoaffective disorder), educational status (rated on a scale from 0–8), employment status, marital status (ever married), family history of schizophrenia, DUP (greater than or less than 1 year), baseline PANSS scores (PANSS total score and previ-

ously described PANSS factor scores[23]), baseline Calgary Depression Scale for Schizophrenia scores, baseline neurologic soft signs (total scores from the Neurological Evaluation Scale[24]), the development of extrapyramidal symptoms other than tardive dyskinesia (a score of ≥ 1 on the Barnes Akathisia Scale and ≥ 14 on the Simpson-Angus Scale at any stage during the study), and tardive dyskinesia. Also, as a measure of acute symptom reduction, we investigated the degree of clinical response at 6 weeks. (We chose 6 weeks, as earlier timepoints did not show significant correlations with outcome.)

Statistical Analyses

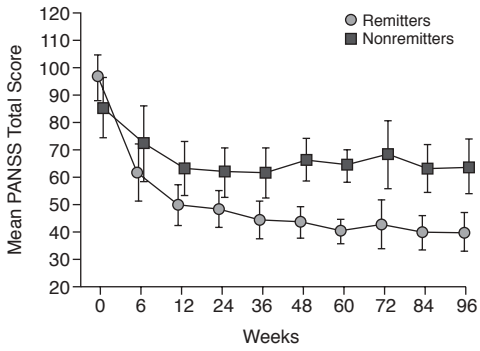
Due to the relatively small sample and the uncertainty regarding the predictive power of the individual variables, we adopted the following procedure to determine the predictive power of the selected variables. First, we split the data into "training" (N = 25) and "test" (N = 16) sets, including only the cases with no missing data (N = 41). For the training set, we drew a random sample (N = 25) with a replacement (bootstrap) sample. We then applied the best-subsets method to the bootstrap sample using discriminant analysis and support vector machines and noted which variables were included in the "best model." Support vector machines are learning machines that can perform binary classification (pattern recognition) and real-valued function approximation (regression estimation) tasks to solve classification and regression problems.[25] These steps were repeated until we were satisfied that clear patterns had emerged. The number of times each variable was included as a predictor determined its predictive power. Based on these findings, a subset of variables was selected, and a final model was constructed for the 25 training cases and tested on the 16 test cases.

All statistical tests were 2-tailed and a 5% ($p < .05$) significance level was set throughout. Results are expressed as the mean ± SD. Where appropriate, 95% confidence intervals are reported.

RESULTS

The sample comprised 57 participants (51% women) aged 28 ± 8.5 years at study entry. Seventy-two percent were diagnosed with schizophrenia, 21% with schizophreniform disorder, and 7% with schizoaffective disorder. The mean DUP was 229 ± 358 days. Subjects were acutely ill at study entry, with a mean PANSS total score of 93.4 ± 16.6. Twenty-eight (49%) completed the 24 months of treatment, the majority as outpatients. Of the 29 who discontinued, 23 were lost to follow-up, 3 were withdrawn due to poor response, 2 relocated, and 1 committed suicide. While 40 (70%) met cross-sectional symptom reduction for remission at some point in the study, only 23 (40%) managed to achieve the full remission criteria when the 6-month duration was applied. Of these 23 subjects, 19 (83%) maintained their remission status throughout the trial. For those attaining it, the mean time to remission was 10 ± 4.13 months. The remission and nonremission groups did not differ significantly regarding the endpoint dose of haloperidol (1.2 ± 0.8 mg vs. 1.8 ± 1.3 mg, respectively, $p = .08$).

Figure 1. Positive and Negative Syndrome Scale (PANSS) Total Scores Over Time for Subjects Meeting Remission Criteria and Subjects Not Meeting Remission Criteria[a,b]



[a]Current effect: F = 7.7000, df = 9,207; p = .00000; repeated-measures analysis of variance. Only patients without missing values are included in this analysis.
[b]Vertical bars denote 95% confidence intervals.

Symptom Improvement Patterns

Figure 1 depicts the mean PANSS total score at each assessment point for the remitted and nonremitted groups separately. Group differences in PANSS total symptom reduction were highly significant ($p < .01$). Both groups showed significant early (baseline to week 6) reductions (remitters, $p < .0001$; nonremitters, $p < .0001$), although the remission group reductions were significantly greater than the nonremission group reductions ($p = .004$). However, whereas the remitting group continued to improve thereafter to endpoint ($p < .01$), the nonremitters failed to do so ($p = .55$). To assess whether these early symptom changes included improvement in "core" psychotic symptoms rather than being just nonspecific treatment effects, we compared composite scores for the 8 PANSS items included in the remission criteria[14] at 6 weeks. Significant reductions were observed in both the remitter ($p < .01$) and nonremitter groups ($p < .01$).

The endpoint PANSS scores for remitters and nonremitters are given in Table 1. PANSS total scores for the remitted and nonremitted groups were 40.7 ± 9.5 and 65.9 ± 20.7 ($p < .01$), respectively. However, there was considerable overlap between the groups, and several nonremitting subjects had lower PANSS total scores than some of the remitters. (Some subjects with a low PANSS total score who did not meet remission criteria had a score of > 3 on just 1 of the PANSS remission items. On

Table 1. Positive and Negative Syndrome Scale (PANSS) Total and Factor Scores at 24 Months for Subjects Who Had Achieved Remission and Subjects Who Had Not Achieved Remission[a]

Score	Remitters	Nonremitters	p Value
PANSS total	40.7 ± 9.5	65.9 ± 20.7	< .01
Negative factor	9.1 ± 3.4	15.4 ± 6.0	< .01
Disorganized factor	6.5 ± 2.2	10.4 ± 3.0	< .01
Psychosis factor	5.1 ± 1.9	10.0 ± 4.6	< .01
Excited factor	4.4 ± 1.0	6.4 ± 3.5	.02
Depression factor	4.5 ± 2.3	4.5 ± 2.2	.90

[a]Values are given as mean ± SD.

the other hand, 1 subject managed to meet the remission criteria with a PANSS total score of 72.) There were highly significant endpoint differences between the remitter and nonremitter groups for the negative, disorganized, and psychosis factor scores. This was, of course, expected, as the remission criteria were specifically selected to represent these 3 symptom domains. However, while the excited factor scores also differed significantly between the groups, the depressive factor scores did not.

Predictors of Remission

Differences between the remitters and nonremitters for the potential predictors that we evaluated are given in Table 2. After inspection of the data, we excluded tardive dyskinesia as a variable because there were too few cases. Guarding against overfitting, the initial best-subsets discriminant analysis identified the following predictors: Neurological Evaluation Scale total score, DUP less than 1 year, marital status, educational status, early treatment response, and PANSS excited factor baseline score. The model was able to correctly predict 92% of the remitters and 85% of the nonremitters in the training set and 89% of the remitters and 86% of the nonremitters in the test set. For the support vector machines verification model, 5 predictors were identified (Neurological Evaluation Scale total score, early treatment response, DUP less than 1 year, marital status, and PANSS excited factor baseline score) that were able to correctly predict 92% of the remitters and 85% of the nonremitters in the training set and 89% of the remitters and 86% of the nonremitters in the test set.

Table 2. Differences Between Remitters and Nonremitters for the Selected Potential Predictor Variables

Potential Predictor	Remitters (N = 19)[a]	Nonremitters (N = 22)[a]	p Value[b]
Gender, male:female, N	10:9	12:10	.90
Race, black:white, N	15:4	16:6	.64
Employed, yes:no, N	12:7	18:4	.18
Ever married, yes:no, N	8:11	5:17	.18
Family history, yes:no, N	7:12	7:15	.74
DUP < 1 year, yes:no, N	18:1	14:8	.01
EPS, yes:no, N	7:12	9:13	.79
TD, yes:no, N	2:17	4:18	.48
PANSS total percent reduction at 6 weeks, mean ± SD	38 ± 17	20 ± 18	.004
Age, y[c]	27 (23 to 32)	32 (28 to 35)	.14
PANSS total baseline score[c]	97 (89 to 104)	91 (84 to 98)	.26
PANSS positive factor score[c]	17 (16 to 18)	16 (15 to 18)	.32
PANSS negative factor score[c]	14 (11 to 17)	14 (11 to 16)	.97
PANSS disorganized factor score[c]	13 (12 to 16)	13 (11 to 15)	.47
PANSS excited factor score[c]	11 (10 to 13)	10 (9 to 11)	.26
CDSS baseline score[c]	3.5 (1.9 to 5.1)	1.3 (0.0 to 2.8)	.05
NES total score[c]	4.6 (2.9 to 6.4)	8.1 (6.5 to 9.8)	< .01
Educational level[c,d]	5.6 (4.7 to 6.4)	5.6 (4.8 to 6.4)	.98
Diagnosis, schizophrenia: schizophreniform/ schizoaffective disorder, N	14:5	19:3	.56

[a]The sample size for the discriminant analysis model was 41.
[b]Analysis of variance and χ^2 test.
[c]Values are given as mean (95% confidence interval).
[d]On a scale of 0 (no schooling) to 8 (postgraduate degree).
Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia, DUP = duration of untreated psychosis, EPS = extrapyramidal symptoms, NES = Neurological Evaluation Scale, PANSS = Positive and Negative Syndrome Scale, TD = tardive dyskinesia.

DISCUSSION

Application of the remission criteria[14] to our sample of first-episode patients demonstrates once again that the overall outcome in schizophrenia is poor, despite a favorable initial treatment response.[8,10] The fact that 70% of all our subjects achieved the cross-sectional symptom reduction criteria for remission at some time attests to the efficacy of antipsychotic treatment in first-episode schizophrenia in the acute setting.[13] However, considerably fewer than half managed to maintain these criteria for 6 months, and even fewer until the completion of the trial, highlighting the need for improved maintenance strategies in the early course of the illness.

Although both groups showed early (6-week) symptom improvement, including core psychotic symptoms, even at this stage there were significant differences between patients who later achieved remission and those who did not. This is consistent with other studies showing a significant relationship between early symptom reduction and later outcome.[8,9] While previous studies used earlier timepoints to assess acute response in relation to later outcome,[3,9] we chose 6 weeks, as some first-episode patients appear to take longer to respond to treatment.[26] This has implications for practice guidelines recommending the duration of treatment trials and suggests that clinicians need to persist longer with a particular treatment in the case of first-episode psychosis.

The differences in symptom profiles at endpoint between remitters and nonremitters are of interest. As expected, significant differences were found in PANSS total scores at endpoint. However, the considerable overlap between the remitters and nonremitters shows that patients who improve on core symptoms may still have other re-

sidual symptoms requiring attention. The significance of this finding needs to be investigated further. Particularly, the persistence of some depressive symptoms in remitted patients challenges the proposal that depression is one of the core symptoms of schizophrenia, insofar as it does not respond to antipsychotic treatment.[27] Also, these "post-psychotic" depressive symptoms are likely to require clinical intervention, considering their association with poor social and vocational functioning[28] and increased risk of relapse.[29]

Our discriminate-analysis findings suggest that a combination of certain baseline and early-clinical-response variables may be useful to clinicians in predicting outcome at an early stage of treatment. The predictor variables identified in our study were generally not unanticipated, as they have previously been linked with treatment outcome. The association between DUP and remission is consistent with many, although not all, other studies showing a longer DUP to be associated with poorer outcome[30–33]; neurologic soft signs have been associated with poor treatment outcome[5]; higher educational status and positive marital status, as measures of good premorbid adjustment, have been associated with a more favorable outcome[34]; and finally, early treatment response is well known to correlate strongly with later outcome.[2,35] As was the case in a previous longitudinal study of patients with chronic schizophrenia, we failed to find significant associations between baseline psychopathology (other than the excitement/hostility factor) and outcome.[8]

In terms of their clinical usefulness, the predictor variables identified in our study are all easy to assess. In the future, other variables not identified in this study may further refine our ability to predict treatment outcome. Strengths of this study are the uniform treatment protocol that was followed for all participants, the relatively long duration of follow-up, and the fact that all subjects were assessed by the same investigator (P.P.O.). The study was limited by its post hoc nature and the relatively small sample, compounded by the high attrition rate accompanying long-term studies such as this one. Also, no attempt was made to assess the role of compliance in our subjects. Given the high levels of nonadherence and partial adherence to medication in first-episode samples,[36] persistent symptoms in the nonremitted subjects in our study could in part be explained on this basis. This is further supported by the finding that some previously "stable" nonremitted patients achieved symptom remission after receiving "ensured" medication delivery in the form of long-acting risperidone injection.[37] A further potential limitation is that this was a flexible-dose study, and we did not investigate a possible role for dose of medication. However, the fact that both predictor models produced similar results suggests that the accurate prediction of remission and nonremission based on the selected variables may be possible. Also, future studies should investigate the relationships between these operationally defined remission criteria and other measures of outcome.

In conclusion, this study provides further evidence that in spite of a good initial response to antipsychotic medication, most patients do not maintain a state of sustained symptom improvement after a first episode of psychosis. Our findings also suggest that a combination of certain clinical and early-treatment-response variables may be useful in predicting later remission.

Drug name: risperidone long-acting injection (Risperdal Consta).

REFERENCES

1. Gaebel W. Prediction of response to acute neuroleptic treatment in schizophrenia. Int Clin Psychopharmacol 1996;11(suppl 2):47–54
2. Correll CU, Malhotra AK, Kaushik S, et al. Early prediction of antipsychotic response in schizophrenia. Am J Psychiatry 2003;160:2063–2065
3. Robinson DG, Woerner MG, Alvir JM, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry 1999;156:544–549
4. Chatterjee A, Chakos M, Koreen A, et al. Prevalence and clinical correlates of extrapyramidal signs and spontaneous dyskinesia in never-medicated schizophrenic patients. Am J Psychiatry 1995;152:1724–1729
5. Arango C, Kirkpatrick B, Buchanan RW. Neurological signs and the heterogeneity of schizophrenia. Am J Psychiatry 2000;157:560–565
6. Murray RM, Van Os J. Predictors of outcome in schizophrenia. J Clin Psychopharmacol 1998;18:2S–4S
7. Ucok A, Polat A, Genc A, et al. Duration of untreated psychosis may predict acute treatment response in first-episode schizophrenia. J Psychiatr Res 2004;38:163–168
8. Breier A, Schreiber JL, Dyer J, et al. National Institute of Mental Health longitudinal study of chronic schizophrenia: prognosis and predictors of outcome. Arch Gen Psychiatry 1991;48:239–246
9. Ribeiro SC, Tandon R, Ricoy R, et al. Clinical predictors of 1-year outcome in schizophrenia. Psychopathology 1992;25:331–334
10. Robinson DG, Woerner M, McMeniman M, et al. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry 2004;161:473–479
11. Schooler N, Rabinowitz J, Davidson M, et al. Risperidone and haloperidol in first episode psychosis: a long-term randomized trial. Am J Psychiatry 2005;162:947–953
12. Csernansky JG, Mahmoud R, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med 2002;346:16–22
13. Lieberman J, Jody D, Geisler S, et al. Time course and biologic correlates of treatment response in first-episode schizophrenia. Arch Gen Psychiatry 1993;50:369–376
14. Andreasen NC, Carpenter WT Jr, Kane JM, et al. Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry 2005;162:441–449
15. Oosthuizen P, Emsley RA, Turner J, et al. Determining the optimal dose of haloperidol in first-episode psychosis. J Psychopharmacol 2001;15:251–255
16. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
17. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), Second Edition. New York, NY: New York State Psychiatric Institute, Biometrics Research; 1994
18. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–267
19. Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. Br J Psychiatry Suppl 1993;39–44
20. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:534–537

21. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
22. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19
23. Emsley R, Rabinowitz J, Torreman M. The factor structure for the Positive and Negative Syndrome Scale (PANSS) in recent-onset psychosis. Schizophr Res 2003;61:47–57
24. Buchanan RW, Heinrichs DW. The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. Psychiatry Res 1989;27:335–350
25. Hastie T, Tibshirani R, Friedman J. The Elements of Statistical Learning. New York, NY: Springer; 2001:371–379
26. Emsley R, Rabinowitz J, Medori R. Time course for antipsychotic treatment response in first-episode schizophrenia. Am J Psychiatry 2006;163:743–745
27. Koreen AR, Siris SG, Chakos M, et al. Depression in first-episode schizophrenia. Am J Psychiatry 1993;150:1643–1648
28. Mandel MR, Severe JB, Schooler NR, et al. Development and prediction of postpsychotic depression in neuroleptic-treated schizophrenics. Arch Gen Psychiatry 1982;39:197–203
29. Birchwood M, Mason R, MacMillan F, et al. Depression, demoralization and control over psychotic illness: a comparison of depressed and non-depressed patients with a chronic psychosis. Psychol Med 1993;23: 387–395
30. Norman RM, Malla AK. Duration of untreated psychosis: a critical examination of the concept and its importance. Psychol Med 2001;31: 381–400
31. Loebel AD, Lieberman JA, Alvir JM, et al. Duration of psychosis and outcome in first-episode schizophrenia. Am J Psychiatry 1992;149: 1183–1188
32. Larsen TK, Moe LC, Vibe-Hansen L, et al. Premorbid functioning versus duration of untreated psychosis in 1 year outcome in first-episode psychosis. Schizophr Res 2000;45:1–9
33. Malla AK, Norman RM, Manchanda R, et al. One year outcome in first episode psychosis: influence of DUP and other predictors. Schizophr Res 2002;54:231–242
34. Perkins D, Lieberman J, Gu H, et al. Predictors of antipsychotic treatment response in patients with first-episode schizophrenia, schizoaffective and schizophreniform disorders. Br J Psychiatry 2004;185: 18–24
35. Stern RG, Kahn RS, Davidson M. Predictors of response to neuroleptic treatment in schizophrenia. Psychiatr Clin North Am 1993;16:313–338
36. Coldham EL, Addington J, Addington D. Medication adherence of individuals with a first episode of psychosis. Acta Psychiatr Scand 2002;106: 286–290
37. Lasser RA, Bossie CA, Gharabawi GM, et al. Remission in schizophrenia: results from a 1-year study of long-acting risperidone injection. Schizophr Res 2005;77:215–227

