

Psychopathology and treatment responsiveness of patients with first-episode schizophrenia

Eva Češková
Radovan Příkryl
Tomáš Kašpárek
Marta Ondrušová

Department of Psychiatry, Masaryk
University and Faculty Hospital Brno,
Czech Republic

Abstract: One hundred and four male patients hospitalized for the first time with the diagnosis of first-episode schizophrenia were comprehensively assessed on admission and discharge. Psychopathology, treatment response, and remission rates were evaluated (based on the Positive and Negative Syndrome Scale (PANSS), severity of symptoms only). On admission, the most frequently observed symptoms were lack of judgment and insight (87.6%), suspiciousness/feelings of persecution (82.3%), delusions (77%), poor attention (70%), disturbance of volition (65.4%), conceptual disorganization (64.7%), and active social avoidance (64%). Except for delusions and hallucinations, the positive items of the PANSS correlated significantly with negative symptoms, and conceptual disorganization correlated with the greatest number of negative symptoms. Individual negative symptoms were present in about half the patients. At discharge, the most frequent symptoms were again lack of judgment and insight (in 55.7%), and for negative symptoms they were blunted affect (22.1%), emotional withdrawal (21.2%), and passive/apathetic social withdrawal (19.5%). The positive symptoms of suspiciousness/feelings of persecution and grandiosity persisted in 20.6% of patients. On average, all symptoms were significantly reduced 44 days after admission. The negative symptoms improved less, compared with the positive ones. At discharge there was a high rate of responders (response defined as minimal 30% reduction of total PANSS): 73% and 74% of patients fulfilled the criteria for remission. On admission, the responders (n=76) had significantly higher scores of most symptoms, both positive and negative ones than nonresponders (n=28).

Keywords: first-episode schizophrenia, treatment response, psychopathology, remission

Introduction

Studying drug-naive, first-episode patients has several advantages, including the opportunity to assess symptoms and signs of illness before the confounding effects of treatment, which ultimately are difficult to disentangle from the effects of illness progression. The investigation of responses to medication offers similar advantages. The small number of clinical trials exploring first-episode schizophrenia leaves a gap between evidence-based and practice-based management. The available data indicate that in first-episode patients, positive symptoms, including hallucinations and delusions, will most often remit with antipsychotic treatment. According to Bradford et al (2003), estimates of the proportion of first-episode patients responding to acute antipsychotic treatment vary from 29% to 96%. The variance in response rates in these studies is related to a number of factors, but most importantly to the duration of the antipsychotic trial, the definition of response, and the drug administered.

The treatment of patients with first-episode schizophrenia has specific features. Compared with later stages of the disease, the first episode is characterized by a more pronounced drug response. Furthermore, both positive and negative symptoms

Correspondence: Eva Češková
Department of Psychiatry, Masaryk
University and Faculty Hospital Brno,
Jihlavská 20, Brno-Bohunice, 625 00 Brno,
Czech Republic
Tel +42 5 3223 2053
Fax +42 5 3223 3706
Email eceskova@fnbrno.cz

improve. Low doses of antipsychotics, ie, 2–6 mg of haloperidol or its equivalent, are effective and patients are more sensitive to extrapyramidal side effects (Remington et al 1998). Atypical antipsychotics represent a great advance in the treatment of first-episode schizophrenia, as there is strong evidence for greater tolerability with equal or better therapeutic efficacy. Still, many patients optimally treated with atypicals are not able to return to their premorbid functioning and experience significant and persistent morbidity.

The Department of Psychiatry of Brno has long-standing experience with patients suffering from first-episode schizophrenia. In addition to a detailed clinical evaluation and a neurological examination focused on soft neurological signs; endocrine, neuroanatomical, and functional brain parameters are monitored and cognitive dysfunction is evaluated (Češková et al 2002). This article reports the results of the response of patients with first-episode schizophrenia to treatment based on the psychopathology of the initial treatment phase. The objectives of the study were: (1) to assess in detail the psychopathology before and after the acute antipsychotic treatment; and (2) to evaluate the response to short-term treatment.

Methods

Subjects

Male patients consecutively hospitalized between November 1997 and March 2004 in the psychotic ward of the Department of Psychiatry were included if they: (1) were experiencing their first admission for first-episode schizophrenia (according to ICD-10); (2) provided written informed consent; and (3) were drug-naïve or had a maximum of four weeks of cumulative exposure to antipsychotic treatment before admission. The exclusion criteria included a history of drug abuse, evidence of organic brain disorder including mental retardation, severe somatic disease, or premature discharge before completing inpatient treatment. The history of previous psychopharmacological treatment was carefully documented in interviews with each patient and the patients' relatives.

ICD-10 diagnoses were made on the basis of a comprehensive assessment of symptoms and history and all other available information about the patients. The diagnosis was confirmed by consensus of two psychiatrists during separate interviews.

Clinical assessment

The psychic state of the patients using the Positive and Negative Syndrome Scale (PANSS; Kay et al 1987) was evaluated after admission (before treatment) and at discharge. Patients meeting inclusion criteria completed a semistructured interview for PANSS with two of the authors (RP and MO rated approximately half the patients each). High interrater reliability for clinical assessment was repeatedly confirmed during raters' participation in international multicenter clinical trials and in regular training sessions at the psychiatric department performed by a skilled clinical researcher (first author EC). The study was designed as an open study. The patients' psychopathology was evaluated on admission, before they started antipsychotic treatment, and on discharge. The response rate (defined as minimally 30% reduction from baseline in the PANSS total score) and achievement of symptomatic remission was also evaluated on discharge. The criteria used were PANSS based, including only severity not duration. The score of 3 (mild) or less was required on all eight of the following PANSS items: P1 delusions, P2 conceptual disorganization, P3 hallucinatory behaviour, G5 mannerisms and posturing, G9 unusual thought content, N1 blunted affect, N4 passive/apathetic social withdrawal, and N6 lack of spontaneity and flow of conversation (Kane 2003).

Treatment

Following baseline assessment on admission, all patients were treated openly by monotherapy with an antipsychotic chosen by the patient's treating clinician. Since becoming available in the Czech Republic, risperidone has been the first drug choice. Other choices were made according to clinical judgment and drug availability. The only concomitant treatments allowed were benzodiazepines for tension, anxiety, and insomnia, and biperidene for extrapyramidal symptoms. The medication was administered by psychiatric nurses to ensure medication adherence.

Data analysis

The statistical analysis was made by comparison of sample means (the paired t-test for comparison of data after admission and before discharge, and t-test for comparison of responders and nonresponders). For correlations between the positive and negative symptoms the Spearman correlation coefficient was used.

Results

Study sample

The study included 104 male inpatients suffering from first-episode schizophrenia according to ICD-10. Their average age was 23.3 (SD 5.7) years. The mean duration of index hospitalization was 44.5 (SD 15.3) days. The mean length of illness, determined from the time the patients first exhibited illness-related behavioral symptoms, was 0.77 (SD 1.0) years. Twenty-eight patients were treated with classical antipsychotics, 64 with risperidone, and 12 with other second generation antipsychotics (atypicals). The mean dose of risperidone was 3.7 (SD 1.2) mg or 218.4 (SD 93) mg chlorpromazine equivalents daily (Woods 2003).

Psychopathology and treatment responsiveness

Psychopathology on admission, discharge, and during treatment is shown in Table 1. Scores for all symptoms decreased significantly before discharge, on average 44 days after admission. We identified 76 responders and 28 nonresponders.

In a categorical analysis of response rate, the proportion of study subjects responding at discharge was 73%; and 74% of patients fulfilled the criteria of remission.

On admission, responders compared with nonresponders had significantly higher scores of 21 individual items out of 30 items (NS difference, P3 hallucinatory behavior, P5

Table 1 Psychopathology according to the PANSS in patients with first-episode schizophrenia (n = 104)

Measure	Admission		Discharge			Admission presence (%)	Discharge presence (%)
	mean	SD	mean	SD	p-values		
P1 delusions	4.5	1.7	1.6	0.9	<0.001	77.0	9.7
P2 conceptual disorganization	3.9	1.5	1.8	1.0	<0.001	64.7%	13.3
P3 hallucinatory behavior	3.5	1.8	1.2	0.6	<0.001	59.3	9.7
P4 excitement	2.5	1.6	1.2	0.6	<0.001	28.3	8
P5 grandiosity	1.9	1.4	1.3	0.7	<0.001	25.7	20.6
P6 suspiciousness/persecutions	4.4	1.2	2.1	0.9	<0.001	82.3	20.6
P7 hostility	1.8	1.3	1.1	0.3	<0.001	16.8	8
Positive subscale PANSS	22.5	6.5	10.3	3.3	<0.001		
N1 blunted affect	3.3	1.5	2.6	1.0	<0.001	44.3	22.1
N2 emotional withdrawal	3.8	1.4	2.6	1.0	<0.001	62	21.2
N3 poor rapport	3.6	1.6	2.4	1.1	<0.001	46	15.9
N4 passive/apathetic social withdrawal	3.8	1.6	2.5	1.1	<0.001	57.5	19.5
N5 difficulty in abstract thinking	4.2	1.8	2.4	1.2	<0.001	64.6	17.7
N6 lack of spontaneity and flow of conversation	3.5	1.7	2.2	1.1	<0.001	52.2	14.1
N7 stereotyped thinking	3.9	1.4	2.4	1.0	<0.001	64.6	18.6
Negative subscale PANSS	26.1	8.8	17.2	6.0	<0.001		
G1 somatic concern	2.6	1.8	1.7	0.9	<0.001	31.8	11.5
G2 anxiety	2.9	1.5	1.4	0.8	<0.001	38	8.8
G3 guilt feelings	1.9	1.3	1.4	0.9	0.0038	24.8	12.4
G4 tension	2.8	1.4	1.4	0.7	<0.001	27.4	8.8
G5 mannerisms and posturing	2.3	1.4	1.6	1.0	<0.001	23.9	11.5
G6 depression	2.4	1.4	1.8	1.0	<0.001	30	14.2
G7 motor retardation	2.6	1.5	2.2	1.0	0.014	37.2	17.7
G8 uncooperativeness	2.7	1.8	1.2	0.6	<0.001	32.8	8.8
G9 unusual thought content	3.5	1.3	1.8	0.8	<0.001	53.0	8
G10 disorientation	2.0	1.4	1.0	0.3	<0.001	27.4	8
G11 poor attention	4.1	1.2	2.6	0.8	<0.001	70	15
G12 lack of judgment and insight	4.8	1.3	3.4	1.0	<0.001	87.6	55.7
G13 disturbance of volition	3.8	1.2	2.6	1.0	<0.001	65.4	21.2
G14 poor impulse control	1.9	1.3	1.1	0.4	<0.001	19.9	8
G15 preoccupation	3.8	1.4	2.3	1.0	<0.001	60	15.9
G16 active social avoidance	3.7	1.4	2.2	1.0	<0.001	64	11.5
General subscale PANSS	48.1	11.7	30.0	8.0	<0.001		
Total score PANSS	96.7	22.4	57.6	15.1	<0.001		

NOTE: symptom presence—score minimally 4 for individual items; NS—significant level > 0.1.

Abbreviations: PANSS, Positive and Negative Syndrome Scale.

grandiosity, P7 hostility, G1 somatic concern, G2 anxiety, G3 guilt feelings, G4 tension, G6 depression, G7 motor retardation). Conversely, at discharge the nonresponders had significantly higher scores of individual symptoms with the exception of P4 excitement, P5 grandiosity, P7 hostility, G3 guilt feelings, G5 mannerisms and posturing, and G14 poor impulse control; ie, the significantly higher psychopathology was observed in 25 out of 30 items (see Table 2).

Association between positive and negative symptoms

Delusions and hallucinations did not correlate significantly with negative symptoms. A significant positive correlation

was found between conceptual disorganization and emotional and social withdrawal, poor rapport, difficulty in abstract thinking, and lack of spontaneity and stereotyped thinking. Significant negative correlation was found between excitement and blunted affect, and emotional and social withdrawal; and significant positive correlation was found between excitement, difficulty in abstract thinking, and stereotyped thinking. Significant negative correlation was observed between grandiosity and blunted affect and lack of spontaneity; and positive correlation was observed between grandiosity and difficulty in abstract thinking.

Suspiciousness and hostility correlated significantly with difficulty in abstract and stereotyped thinking, and hostility correlated significantly with poor rapport (see Table 3).

Table 2 Comparison of symptoms in responders and nonresponders (mean values)

Measure	Admission					Discharge				
	Responder		Nonresponder		p-values	Responder		Nonresponder		p-values
	mean	SD	mean	SD		mean	SD	mean	SD	
n	76		28			76		28		
P1 delusions	4.8	1.8	4.0	1.4	0.0445	1.5	0.8	2.1	1.0	0.0026
P2 conceptual disorganization	4.3	1.4	2.9	1.2	<0.001	1.6	0.8	2.4	1.1	<0.001
P3 hallucinatory behavior	3.7	1.8	3.0	1.7	NS	1.1	0.3	1.6	0.9	<0.001
P4 excitement	2.7	1.7	1.8	1.0	0.0186	1.1	0.5	1.4	0.8	NS
P5 grandiosity	2.0	1.5	1.5	1.0	NS	1.2	0.6	1.5	1.0	NS
P6 suspiciousness/persecutions	4.5	1.2	3.9	1.0	0.0223	1.9	0.8	2.6	0.9	<0.001
P7 hostility	1.9	1.4	1.5	0.7	NS	1.0	0.3	1.2	0.4	NS
Positive subscale PANSS	24.0	6.6	18.6	3.4	<0.001	9.4	2.5	12.7	3.9	<0.001
N1 blunted affect	3.5	1.6	2.6	1.1	0.005	2.3	1.0	3.2	0.8	<0.001
N2 emotional withdrawal	4.0	1.6	3.2	0.8	0.0223	2.4	1.0	3.3	0.6	<0.001
N3 poor rapport	4.0	1.7	2.6	0.8	<0.001	2.1	1.0	3.2	1.0	<0.001
N4 passive/apathetic social withdrawal	4.0	1.6	3.2	1.1	0.0160	2.2	1.0	3.2	0.9	<0.001
N5 difficulty in abstract thinking	4.7	1.8	3.0	1.4	<0.001	2.2	1.2	2.9	1.0	0.0059
N6 lack of spontaneity and flow of conversation	3.8	1.8	2.7	1.1	0.0036	2.0	1.0	2.8	1.2	0.0022
N7 stereotyped thinking	4.1	1.5	3.3	0.9	0.0135	2.1	0.9	3.2	0.7	<0.001
Negative Subscale PANSS	28.1	9.1	20.6	4.8	<0.001	15.6	5.5	21.8	4.5	<0.001
G1 somatic concern	2.8	2.0	2.1	1.0	NS	1.5	0.9	2.0	1.0	0.0228
G2 anxiety	2.9	1.6	2.8	1.1	NS	1.3	0.7	1.7	1.0	0.0163
G3 guilt feelings	1.9	1.4	1.8	1.2	NS	1.4	0.8	1.6	1.2	NS
G4 tension	2.9	1.5	2.5	1.1	NS	1.3	0.6	1.7	0.9	0.0068
G5 mannerisms and posturing	2.5	1.4	1.7	1.0	0.0112	1.5	0.9	1.9	1.0	NS
G6 depression	2.4	1.5	2.5	1.4	NS	1.6	0.9	2.2	1.1	0.0061
G7 motor retardation	2.6	1.6	2.8	1.1	NS	2.0	1.0	2.7	0.9	<0.001
G8 uncooperativeness	3.0	2.0	1.7	0.9	0.0014	1.1	0.4	1.5	0.8	0.0052
G9 unusual thought content	3.8	1.3	2.9	1.0	0.0019	1.7	0.8	2.2	0.8	0.0059
G10 disorientation	2.2	1.5	1.3	1.1	0.0045	1.0	0.0	1.2	0.5	0.0050
G11 poor attention	4.5	1.2	3.4	0.7	<0.001	2.5	0.8	3.0	0.7	0.0020
G12 lack of judgment and insight	5.1	1.3	4.2	1.0	0.0037	3.3	1.0	3.8	0.8	0.0078
G13 disturbance of volition	4.0	1.2	3.2	1.1	0.0042	2.3	0.9	3.1	1.1	<0.001
G14 poor impulse control	2.1	1.4	1.4	0.7	0.0145	1.1	0.4	1.2	0.6	NS
G15 preoccupation	4.1	1.4	3.0	1.0	<0.001	2.1	0.9	3.0	0.8	<0.001
G16 active social avoidance	4.0	1.5	3.0	0.9	0.0016	2.0	0.8	2.8	0.8	<0.001
General subscale PANSS	51.0	11	40.4	7.6	<0.001	27.8	6.6	35.9	8.2	<0.001
Total Score PANSS	103.1	22	79.7	12.6	<0.001	52.7	12	70.6	14.2	<0.001

NOTE: symptom presence–score minimally 4 for individual items; NS—significant level > 0.1.

Abbreviations: Resp responders; nonresp, nonresponders; PANSS, Positive and Negative Syndrome Scale.

Table 3 Correlations between positive and negative symptoms (Spearman correlation)

	N1 blunted affect	N2 emotional withdrawal	N3 poor rapport	N4 passive/apathetic social withdrawal	N5 difficulty in abstract thinking	N6 lack of spontaneity and flow of conversation	N7 stereotyped thinking
P1 delusions	-0.05	-0.11	-0.06	-0.07	0.14	-0.07	0.04
P2 conceptual disorganization	0.13	0.21 ^a	0.46 ^a	0.23 ^a	0.62 ^a	0.29 ^a	0.56 ^a
P3 hallucinatory behavior	-0.01	0.08	0.10	0.05	0.00	0.09	0.02
P4 excitement	-0.34 ^a	-0.24 ^a	-0.01	-0.24 ^a	0.41 ^a	-0.16	0.21 ^a
P5 grandiosity	-0.25 ^a	-0.08	-0.09	-0.16	0.23 ^a	-0.21 ^a	0.07
P6 suspiciousness/persecutions	-0.02	0.17	0.18	0.17	0.24 ^a	0.11	0.30 ^a
P7 hostility	-0.17	0.12	0.28 ^a	0.15	0.34 ^a	0.18	0.24 ^a

^a $p < 0.05$

Discussion

This study is unique in its detailed evaluation of individual symptoms in patients experiencing first-episode schizophrenia. Observed psychopathology on positive subscale of PANSS at the initial assessment demonstrated the highest occurrence of suspiciousness/feelings of persecutions (82.3%), delusions (77%), conceptual disorganization (64.7%), and hallucinatory behavior (59.3%). Excitement, grandiosity and hostility were less frequent. All negative symptoms were present in about half the patients. The negative symptoms present in first hospitalized, drug-naïve patients could be considered as primary negative symptoms (Peralta et al 2000). In a methodologically sound study, Peralta came to the conclusion, that negative symptoms rated during a first psychotic episode before and after starting antipsychotic treatment are mainly primary in character, and should be considered as a direct manifestation of the basic dysfunctions of schizophrenia. The high scores of negative symptoms, although it exceeds numerically the positive symptom score, is comparable with previously published studies that assessed symptoms by means of the PANSS and gave initial values (Sanger et al 1999; Oosthuizen et al 2004). In our sample, the most frequent general symptoms were lack of judgment and insight (87.6%), poor attention (70%), disturbance of volition (65.4%), active social avoidance (64%), preoccupation (60%), and unusual thought content (53%). Overall, the most frequently observed symptoms after admission were lack of judgment and insight and suspiciousness/feelings of persecutions.

At discharge, lack of judgment and insight was present in 55.7% of patients. As for negative symptoms, blunted affect was present in 22.1% of patients, emotional withdrawal in 21.2%, and passive/apathetic social withdrawal in 19.5% of patients. As for positive symptoms,

suspiciousness/feelings of persecutions persisted in 20.6% and grandiosity in 20.6% of patients. The high percentage of patients with lack of judgment and insight could contribute to the well known fact that patients with first-episode schizophrenia are highly noncompliant. Coping with first-episode schizophrenia may be similar to that seen in patients with serious somatic diseases, where denial is one of the first phases. Despite a favorable acute response profile, first-episode patients have been shown to experience a high rate of psychotic relapse, particularly if they have discontinued antipsychotic medication (Gitlin et al 2001).

As for the treatment response, our results are consistent with those of prior studies of patients with first-episode schizophrenia that have found favorable rates of therapeutic response to antipsychotic drugs. In our sample a statistically significant improvement of both positive and negative symptoms was observed, but the reduction was less marked for negative symptoms. Most studies of first-episode schizophrenia report that the reduction of positive symptoms is faster and more complete, and negative symptoms usually persist in a mild form (Remington et al 1998; Bradford et al 2003; Oosthuizen et al 2004). The influence on negative symptoms in studies with the same acute treatment duration (6 weeks) was minor compared with the influence on positive symptoms and it was comparable with our results. The mean dose used in our patients is in agreement with observations suggested that first-episode patients may be more sensitive to the pharmacologic effects of antipsychotic drugs and may thus require lower drug doses (McEvoy et al 1991; Remington et al 1998).

In a categorical analysis of the response rate, in a 6-week, randomized, controlled trial comparing the effects of risperidone with those of haloperidol, the response rates were 63% for risperidone and 56% for haloperidol (Emsley 1999). In another double-blind, 6-week acute treatment

study comparing olanzapine and haloperidol, the rate of clinical response was significantly higher for the olanzapine-treated patients (67.2%) than for the haloperidol-treated patients (29.2%) (Sanger et al 1999). A recently published study comparing clozapine and chlorpromazine in patients with first-episode schizophrenia and schizophreniform disorder reported response rates of 62% for clozapine and 50% for chlorpromazine (Lieberman, Phillips, et al 2003). Finally, in a double blind study the proportion of study subjects responding by week 12 was 55% for those assigned to olanzapine, compared with 46% for those receiving haloperidol (Lieberman, Tollefson, et al 2003). The response rate in the present study was 73%. The difference may be explained by the sample characteristics and methods. In the present sample, mostly drug-naïve patients were included, the study was open, and medications were individualized with the potential to change the antipsychotic according to the psychic state. Although the response criteria of all these studies varied, overall the results indicate that patients with first-episode psychosis are highly responsive to antipsychotic drug treatment, with a trend suggesting that atypical drugs exhibit some degree of superiority over typicals in response rate and time to response. Most of our patients were also treated with atypical antipsychotics. Our expectations of treatment outcomes for patients are evolving. Remission is now a realistic goal. Patients in symptomatic remission will benefit most from psychosocial interventions. A substantial part of our patients fulfilled not only the response criteria but also suggested criteria for remission.

In responders we found a significantly higher score on both positive and negative symptoms before treatment including the lack of judgment and insight. Responders had higher scores of initial psychopathology than nonresponders. A marked improvement in responders probably enabled them to understand better that the previous condition had been pathological and they experienced a clear difference between the previous condition and the outcome of acute treatment, thus improving their chance of creating insight. Also the symptoms associated with the cognitive function level (attention, thinking) improved more significantly and they were able to understand better their own personal realities. In the literature, the severity of basal symptomatology and the early change of symptomatology were considered to be predictors of treatment response. But no single factor was a strong prediction factor. A combination of the factors seemed to be more promising (Awad et al 1994; Češková et al 2002). Of interest is also the association

between conceptual disorganization and negative symptoms. Possibly, marked disorganization of thinking leads to problems in the contact with reality and in communication. We have not found any study that deals with such aspects of first-episode schizophrenia.

The findings are limited by the fact that the study was open and performed under routine clinical conditions. Not all patients were treated according to the standard algorithm. However, our results provide a closer look at the psychopathological profile of patients with first-episode schizophrenia and confirm that at this stage of illness there is a capacity for early and substantial improvement of symptoms. The persistent lack of judgment and insight in about half of patients is a challenge for health professionals and calls for early psychological care and alleviation of psychotic symptoms.

Conclusions

On average there is a broad spectrum of psychopathology, positive, (primary) negative, and less specific general symptoms present in most patients with first-episode schizophrenia. Despite patients reacting quickly to antipsychotic treatments, some symptoms (lack of judgment and insight, negative symptoms) persist in some patients and may contribute to function impairment and non-compliance. Patients with severe psychopathology may be more responsive to the acute treatment. Psychiatrists should especially try to influence lack of judgment and insight, which in the early stages of illness are important for its future course.

Acknowledgments

Supported by the Ministry of Education, Czech Republic (project nr CEZ: J07/18/141100001).

References

- Awad AG. 1994. Prediction research of neuroleptic treatment outcome in schizophrenia – state of the art 1978–1993. In Gaebel W, Awad AG (eds). Prediction of neuroleptic treatment outcome in schizophrenia. Concepts and methods. Wien: Springer-Verlag. p 1–14.
- Bradford DW, Perkins DO, Lieberman JA. 2003. Pharmacological management of first-episode schizophrenia and related nonaffective psychoses. *Drugs*, 63:2265–83.
- Češková E, Drybčák P, Lorenc M. 2002. Biological markers and possibilities for predicting therapeutic results in schizophrenia. A methodological contribution. *Prog Neuropsychopharmacol Biol Psychiatry*, 26:683–91.
- Emsley RA. 1999. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study Risperidone Working Group. *Schizophr Bull*, 25:721–9.

- Gitlin M, Nuechterlen K, Subotnik KL, et al. 2001. Clinical outcome following neuroleptic discontinuation in patients with remitted recent-onset schizophrenia. *Am J Psychiatry*, 158:1835–42.
- Kane JM, Leucht S, Carpenter D, et al. 2003. Expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders. Introduction: methods, commentary, and summary. *J Clin Psychiatry*, 64(Suppl 12):5–19.
- Kay S, Fiszbein A, Opler LA. 1987. The positive and negative syndrome scale for schizophrenia. *Schizophr Bull*, 13:261–78.
- Lieberman JA, Phillips M, Gu H, et al. 2003. Atypical and conventional antipsychotic drugs in treatment-naïve first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology*, 28:995–1003.
- Lieberman JA, Tollefson G, Tohen M, et al. 2003. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. *Am J Psychiatry*, 160:1396–404.
- McEvoy JP, Hogarty GE, Steingard S. 1991. Optimal dose of neuroleptic in acute schizophrenia: a controlled study of the neuroleptic threshold and higher haloperidol dose. *Arch Gen Psychiatry*, 48:739–45.
- Oosthuizen P, Emsley R, Turner JH, et al. 2004. A randomized, controlled comparison of the efficacy and tolerability of low and high doses of haloperidol in the treatment of first-episode psychosis. *Int J Neuropsychopharmacol*, 7:121–31.
- Peralta V, Cuesta MJ, Martinez-Larrea A, et al. 2000. Differentiating primary from secondary negative symptoms in schizophrenia: a study of neuroleptic-naïve patients before and after treatment. *Am J Psychiatry*, 157:1461–6.
- Remington G, Kapur S, Zipursky RB. 1998. Pharmacotherapy of first-episode schizophrenia. *Br J Psychiatry*, 172(Suppl 33):66–70.
- Sanger TM, Lieberman JA, Tohen M, et al. 1999. Olanzapine versus haloperidol treatment in first-episode psychosis. *Am J Psychiatry*, 156:79–87.
- Woods SW. 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotic. *J Clin Psychiatry*, 64:663–7.

