Early Intervention IN PSYCHIATRY
First Impact Factor released in June 2010 and now listed in MEDLINE!
International Early Psychosis Association

Early Intervention in Psychiatry 2015; ••: ••–••
doi:10.1111/eip.12266

Brief Report

Duration of untreated psychosis and acute remission of negative symptoms in a South American first-episode psychosis cohort

Alfonso González-Valderrama,[1,2] Carmen Paz Castañeda,[2] Cristián Mena,[2] Juan Undurraga,[2,3] Pilar Mondaca,[2] Matías Yañez,[2] Paula Bedregal[4] and Ruben Nachar[1,2]

[1]Facultad de Medicina, Universidad Finis Terrae, [2]Early Intervention in Psychosis Program, Instituto Psiquiátrico 'Dr José Horwitz Barak', [3]Department of Psychiatry, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, and [4]Departamento de Salud Publica, Pontificia Universidad Católica de Chile, Santiago, Chile

Corresponding author: Dr Alfonso González-Valderrama, Early Intervention in Psychosis Program, Psychiatric Institute 'Dr. José Horwitz Barak', Avenida La Paz 841, Recoleta, Santiago PC 8431621, Chile. Email: aagonzav@uc.cl

Received 25 February 2015; accepted 12 July 2015

Abstract

Aim: To determine the association between duration of untreated psychosis (DUP) and symptoms remission in a hospitalized first-episode psychosis cohort.

Methods: Inpatients with a first-episode non-affective psychosis were recruited. Subjects were divided into two groups of long and short DUP using a 3-month cut-off point, and this was related to remission at 10 weeks of treatment. Multivariate analyses were performed.

Results: Fifty-five inpatients were included. There were no differences in remission rates of positive symptoms. Up to 76.5% of the patients with a short DUP (<3 months) achieved remission of negative symptoms versus 31.6% in the DUP ≥ 3 months group ($P = 0.003$). After controlling for relevant factors, patients with a shorter DUP were still three times more likely to achieve negative symptoms remission (HR: 3.04, 95% CI 1.2–7.5).

Conclusions: DUP is a prognostic factor that should be considered at an early stage to identify a 'high risk' subgroup of persistent negative symptoms.

Key words: duration of untreated psychosis, early intervention, negative symptom, psychosis, schizophrenia.

INTRODUCTION

Duration of untreated psychosis (DUP) is one of the most relevant clinical response predictors in first-episode schizophrenia. It has been considered an independent and potentially modifiable factor affecting prognosis and response to treatment in these patients.[1–4] Reducing DUP decreases disability and suicidality, and it also has favourable effects on negative, cognitive and depressive symptoms on 1, 2 and 5 years of follow up.[5,6] It has also been suggested that a shorter DUP increases the chances of having a better functioning 10 years after the first presentation.[7] Consequently, the World Health Organization and the International Early Psychosis Association recommend that the delay between first-episode psychosis onset and treatment initiation should be smaller than 3 months.[8] However, these recommendations have been based mainly on studies from the developed world, where health services are generally more advanced.[9] Our objective was therefore to help resolve that knowledge gap and determine the clinical effects of DUP (with 3 months as cut-off) in hospitalized first-episode non-affective psychotic disorder patients in an understudied South American setting.

METHODS

We included patients between 15 and 30 years of age with a first episode of non-affective psychosis (schizophrenia or schizophreniform disorder according to DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision) criteria[10]) admitted to the inpatient unit of

the Early Intervention in Psychosis Program between December 2011 and January 2014. This programme belongs to the state-funded Psychiatric Institute 'Dr. José Horwitz B.' in Santiago, Chile, and is a referral service of public health system with a catchment area of 1.000.000 inhabitants. We excluded those with a history of mental retardation. All patients signed an informed consent. For patients younger than 18 years, patient and legal tutors' consent was required. This project was approved by the ethics committee of the Pontificia Universidad Católica de Chile.

Procedures

Patients were assessed by two psychiatrists with a 10-year experience in psychotic disorders every 2 weeks for the first 10 weeks of treatment in order to introduce antipsychotic treatment adequately. Treatments were prescribed following the Chilean guideline for first episode of schizophrenia,[11] which suggests to start with atypical antipsychotics. In addition, patients were offered psychotherapy, psychoeducation and/or occupational therapy. Treatment was determined by the attending psychiatrist, who was not part of the research team.

The main independent variable was the DUP. It was calculated using the Symptom Onset Schizophrenia Inventory (SOS).[12] We used the PANSS scale[13] and its structured interview (SCI-PANSS)[14] to assess positive and negative symptoms. Baseline assessments were performed within the first week of admission. Main outcome was remission rate at 10 weeks, defined as a PANSS score of ≤3 in all subscales according to the Andreasen criteria[15] (because of follow-up time, we could not include 6 months criteria). Other variables previously shown to predict response to treatment were also examined, including age and sex,[16] substance use disorder,[17] and premorbid functioning.[18] The latter was measured using the Cannon-Spoor Premorbid Adjustment Scale (PAS)[19,20] to assess if there was a functioning progressive deterioration nearer the psychotic episode. We also assessed extrapyramidal symptoms as they have been associated to negative symptoms.[21] We used the Simpson-Angus Scale (SAS), considering 0.3 as the threshold for significant symptoms.[22] All raters were trained with video sessions and face interviews for SOS, PANSS, PAS and SAS scales.

Statistical analysis

Data analyses were performed using graphical methods and the Shapiro–Wilk normality test. For

TABLE 1. Baseline and follow-up characteristics of the sample

Baseline characteristics of the sample (n = 55)	
Age, years (mean; SD)	20.2 (2.1)
Male (n, %)	43 (78.2)
Duration of education, years (mean; SD)	11.0 (1.7)
Baseline positive symptoms (sum scores), PANSS (mean; SD)	29.7 (7.6)
Baseline negative symptoms (sum scores), PANSS (mean; SD)	25.7 (10.2)
Duration of untreated psychosis, months (mean; (SD)/median)	10.8 (12.1)/7.3
Substance use disorders (n, %)	25 (45.5)
Childhood premorbid adjustment, PAS (ages 6–11), (mean; SD)†	0.3 (0.18)
Early adolescent premorbid adjustment, PAS (ages 12–15), (mean; SD)†	0.34 (0.17)
Late adolescent premorbid adjustment, PAS (ages 15–18), (mean; SD)†	0.45 (0.21)
Global premorbid adjustment, PAS (mean; SD)†	0.37 (0.17)
Extrapyramidal symptoms, SAS (mean; SD)‡	0.24 (0.29)
Characteristics of the sample at follow up (week 10)	
Diagnose at 10th week	
Schizophrenia (n, %)	36 (65.5)
Schizophreniform disorder (n, %)	19 (35.5)
Number of different antipsychotic trials in the 10-week period (n, %)	
1	19 (34.5)
2	33 (60)
3	3 (5.5)
Extrapyramidal symptoms, SAS (mean; SD)‡	0.19 (0.27)
Risperidone (n, %)	37 (67.3)
Olanzapine (n, %)	36 (65.4)
Aripiprazole	11 (20)
Clozapine (n, %)	7 (12.7)
Electroconvulsive therapy (n, %)	13 (23.6)
Positive symptoms remission, PANSS (n, %)§	43 (78.2)
Negative symptoms remission, PANSS (n, %)§	25 (45.5)
Positive and negative symptoms remission (n, %)§	22 (40)

†Cannon-Spoor Premorbid Adjustment Scale (PAS):[19] a higher score describes a worse premorbid functioning. To calculate a final score, we calculated the total score in each item divided by the maximum possible score ranges from 0 to 1.[19]

‡Simpson-Angus Scale (SAS):[22] considering 0.3 as the threshold for significant symptoms.

§Remission: according to the Andreasen criteria:[15] score of ≤3 on all PANSS subscales looking at positive (delusions, conceptual disorganization, hallucinatory behaviour, mannerisms and posturing, and unusual thought content – P1, P2, P3, G5 and G9) and independently for negative symptoms (blunted affect, passive/apathetic social withdrawal, and lack of spontaneity and flow of conversation – N1, N4 and N6). Because of follow-up time, we could not include 6 months.

PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale; SAS, Simpson-Angus Scale; SD, standard deviation.

univariate analysis, the *t*-test was used for independent and continuous variables. Chi-squared or Fisher test was used for categorical variables. To analyse the association of DUP (defined as a categorical variable: <3 months vs. ≥3 months) on remission of positive and negative symptoms at the 10th week follow up, a survival analysis was performed. To compare the survival curves for the cumulative probability of survival (time to remission), we used a non-parametric log-rank statistical test. Possible confounders or modifiers of the effect of DUP on remission were examined using a Cox proportional hazards model for multivariate analysis, obtaining hazard ratio (HR). Significance level was established at $P < 0.05$. Statistical package SPSS (version 15.0; SPSS Inc., Chicago, IL) was used.

RESULTS

Fifty-five inpatients were included and completed the 10-week follow-up period. Up to 45.5% ($n = 25$) of them completed the evaluation in an outpatient setting. Table 1 shows the main sample characteristics. Mean DUP was 10.8 months (SD: 1.2) with a median of 7.3 months. Up to 67.3% ($n = 37$) of the patients were treated with risperidone (mean dose 4.7 mg day^{-1}, SD 1.5) and 65.4% ($n = 36$) with olanzapine (mean dose of 17.6 mg day^{-1}, SD 5.8). Twenty per cent ($n = 11$) were treated with aripiprazole and 12.7% ($n = 7$) started clozapine. Sixty per cent of the patients ($n = 33$) received two antipsychotics. Up to 78.2% ($n = 43$) of the patients achieved positive symptoms remission and 45.5%

TABLE 2. Distribution of other known baseline predictors of clinical response to antipsychotics in the shorter or longer DUP groups

Baseline predictor	DUP < 3 months ($n = 17$)	DUP ≥ 3 months ($n = 38$)		*P*-values
Age, years (mean; SE)†	20.0 (2.0)	20.3 (2.3)	$t = 0.62$; d.f. = 53	0.54
Male (*n*, %)‡	13 (76.5)	30 (78.9)	$\chi^2 = 0.042$; d.f. = 1	0.84
Duration of education, years (mean; SE)†	11.6 (1.6)	10.8 (1.8)	$t = 1.643$; d.f. = 53	0.1
Baseline positive symptoms (sum scores) (mean; SE)†	30.6 (1.6)	29.3 (1.3)	$t = 0.587$; d.f. = 53	0.56
Baseline negative symptoms (sum scores) (mean; SE)†	23.5 (2.5)	26.7 (1.6)	$t = 1.048$; d.f. = 53	0.3
Substance use disorders (*n*, %)‡	8 (47.1)	17 (44.7)	$\chi^2 = 0.026$; d.f. = 1	0.87
Childhood premorbid adjustment (mean; SE)†§	0.23 (0.15)	0.33 (0.18)	$t = 1.86$; d.f. = 53	0.068
Early adolescent premorbid adjustment (mean; SE)†§	0.26 (0.16)	0.38 (0.16)	$t = 2.35$; d.f. = 53	0.023*
Late adolescent premorbid adjustment (mean; SE)†§	0.3 (0.15)	0.5 (0.2)	$t = 3.67$; d.f. = 33	0.001*
Global premorbid adjustment (mean; SE)†§	0.26 (0.04)	0.4 (0.03)	$t = 2.8$; d.f. = 48	0.007*
Extrapyramidal symptoms, SAS (mean; SE)†¶	0.18 (0.06)	0.27 (0.05)	$t = 1.16$; d.f. = 53	0.25
Clinical variables at follow up	**DUP < 3 months ($n = 17$)**	**DUP ≥ 3 months ($n = 38$)**		***P*-values**
Number of antipsychotics (*n*, %)‡				
1	7 (12.7)	12 (21.8)		
2	9 (16.4)	24 (43.6)		
3	1 (1.8)	2 (3.6)	$\chi^2 = 0.526$; d.f. = 2	0.77
Electroconvulsive therapy (*n*, %)‡	2 (11.8)	11 (28.9)	$\chi^2 = 1.921$; d.f. = 1	0.3
Chlorpromazine equivalent (mean; SE)†	705.9 (80.1)	780.8 (54.1)	$t = 0.77$; d.f. = 53	0.44
Extrapyramidal symptoms, SAS (mean; SE)†,††	0.15 (0.06)	0.21 (0.05)	$t = 0.76$; d.f. = 49	0.45
Positive symptoms remission, PANSS (*n*, %)‡,††	15 (88.2)	28 (73.7)	$\chi^2 = 1.458$; d.f. = 1	0.3
Negative symptoms remission, PANSS (*n*, %)‡,††	13 (76.5)	12 (31.6)	$\chi^2 = 9.547$; d.f. = 1	0.003*

*$P < 0.05$.
†Student's *t*-test
‡Chi-squared or Fisher test.
§Cannon-Spoor Premorbid Adjustment Scale (PAS):[19] a higher score describes a worse premorbid functioning. To calculate a final score, we calculated the total score in each item divided by the maximum possible score ranges from 0 to 1.[19]
¶Simpson-Angus Scale (SAS):[22] considering 0.3 as the threshold for significant symptoms.
††Remission: according to the Andreasen criteria:[15] score of ≤3 on all PANSS subscales looking at positive (delusions, conceptual disorganization, hallucinatory behaviour, mannerisms and posturing, and unusual thought content – P1, P2, P3, G5 and G9) and independently for negative symptoms (blunted affect, passive/apathetic social withdrawal, and lack of spontaneity and flow of conversation – N1, N4 and N6). Because of follow-up time, we could not include 6 months.
PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale; SAS, Simpson-Angus Scale; SE, standard error.

($n = 25$) of them achieved negative symptoms remission.

There was a non-significant difference in remission rates of positive symptoms between patients with a DUP < 3 months and those with a DUP ≥ 3 months (88.2% and 73.7%, respectively; $P = 0.3$). Regarding negative symptoms, 76.5% of patients with a short DUP (<3 months) achieved remission versus 31.6% in the DUP ≥ 3 months group ($P = 0.003$) (Table 2). In addition, we performed a survival analysis which showed faster negative symptom remission rates in the DUP < 3 group (Fig. 1; $P < 0.001$). We then explored the distribution of other potential confounding variables known to affect response rates to antipsychotic treatment in both groups (Table 2). Patients with a shorter DUP had a better premorbid functioning in early adolescence ($P = 0.023$) and late adolescence ($P = 0.001$). There were no statistically significant differences between groups regarding substance abuse, positive and negative symptoms at baseline, use of Electroconvulsive Therapy (ECT) or presence of extrapyramidal symptoms (Table 2).

We finally performed a Cox proportional hazards model exploring the effect of DUP and other variables on negative symptoms remission. We included in our model global premorbid functioning, sex, substance use disorders and extrapyramidal symptoms (Table 3). The model showed that after controlling for all the other factors, patients with a DUP < 3 months were still almost three times more likely to achieve negative symptoms remission than

FIGURE 1. Kaplan–Meier survival analysis. Time to negative symptoms remission in the 10 weeks of follow up in patients with a short DUP (<3 months) and long DUP (≥3 months) (log-rank test, $\chi^2 = 12.74$; d.f. = 1; $P < 0.001$).

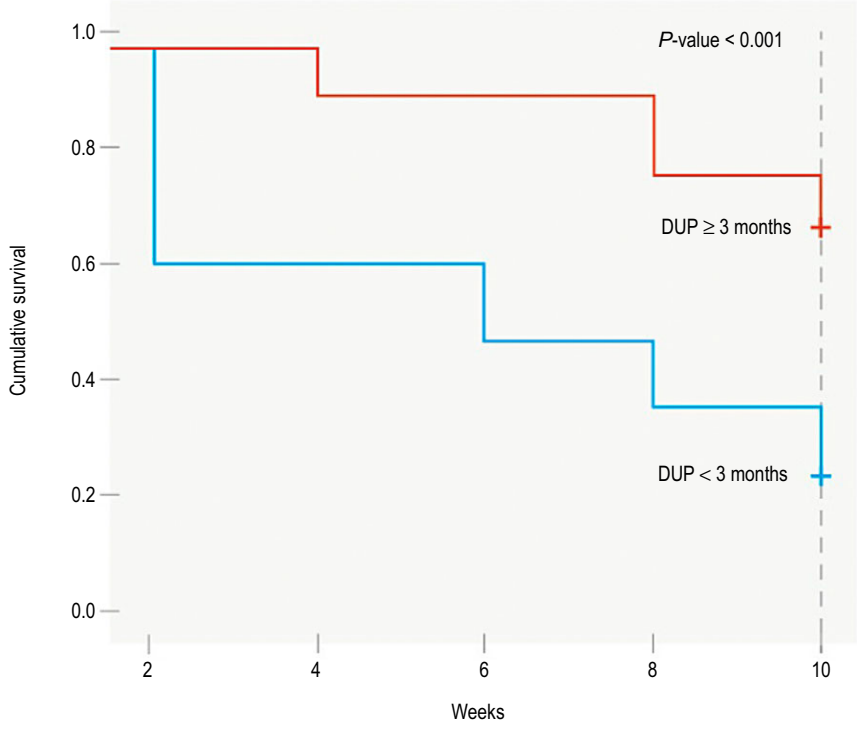

TABLE 3. Cox proportional hazards model with remission of negative symptoms as the dependent variable being predicted

Variables included in the model	β	*P*-values	Exp (B)	95% IC for Exp (B)	
DUP < 3 months	1.26	0.007*	3.52	1.41	8.7
Global premorbid adjustment, PAS	−0.3	0.84	0.74	0.041	13.5
Extrapyramidal symptoms, SAS	−2.96	0.048*	0.054	0.003	0.968
Female gender	2.04	0.002*	7.68	2,17	27.24
Presence of substance use disorders	−0.89	0.096	0.41	0.14	1.17

*$P < 0.05$.
DUP, duration of untreated psychosis; PAS, Premorbid Adjustment Scale; SAS, Simpson-Angus Scale.

those with a DUP ≥ 3 months at 10th week of follow up (HR: 3.52, 95% CI 1.41–8.7; $P = 0.007$). Other factors that significantly predicted remission rates at 10 weeks in our model were gender (favouring being a woman, HR: 7.68, 95% CI 2.17–27.24; $P = 0.002$) and extrapyramidal symptoms (higher scores decreased the likelihood of remission; HR: 0.054, 95% CI 0.003–0.968; $P = 0.048$).

DISCUSSION

We here present the data on the effect of the DUP on remission rates in a South American cohort of patients, which is generally underrepresented in the scientific literature.[9] Our main result was a higher likelihood of negative symptoms remission in patients with a first episode of psychosis and a short DUP, which echoes other observational studies in the developed world[23] and a controlled trial demonstrating a causal link between the two.[24] The association of a short DUP and symptoms persisted after adjusting for possible confounders in the multivariate analysis.

Our sample of included patients displayed high levels of symptoms compared to other studies.[25–27] This is related to the inpatient setting where we recruited our patients, including only subjects requiring inpatient treatment. As such, our results may not be generalizable. Men were also overrepresented in our sample. This is also likely to be due to the inpatient setting, as men tend to have a more severe presentation than women.[28] However, after that consideration, women continue to have a better prognosis than men in our sample.[16,28]

Regarding treatment, a high proportion (23.6%, $n = 13$) of the patients received ECT. This is usually recommended for drug-resistant patients, catatonia, aggression or suicidal behaviour, and when rapid global improvement and reduction of acute symptomatology are required.[29,30] This overrepresentation of ECT could be explained by our highly symptomatic sample. Risperidone and olanzapine were the most frequently used antipsychotics, which is similar to the RAISE study results.[31] Some extrapyramidal symptoms may mimic negative symptoms and should be considered as differential diagnosis.[21] In this regard, higher rates of extrapyramidal symptoms were related to persistent negative symptoms, although after controlling this, DUP still had a significant effect on them.

Our findings confirm that patients with a longer DUP may be considered as a 'high risk' subgroup for exhibit-persistent negative symptoms. Moreover, they reinforce the idea that DUP reduction should be one of the main objectives of early intervention in psychosis programmes. Considering the scarce evidence on drug treatments, early interventions should focus on psychosocial interventions.[32]

The limitations of this study include a small inpatient sample size that might not be generalizable. As an observational study, it only allows to infer relationships between variables and does not give information about causality. We did not include any interrate reliability measure. Lastly, 10 weeks is a short period to assess longitudinal course.

In conclusion, our study reinforces the idea that DUP is an important prognostic factor that should be considered at an early stage by clinicians as a routine clinical evaluation. This would allow teams to identify a 'high risk' group of poor prognosis patients on whom more interventions and resources should be allocated.

ACKNOWLEDGEMENTS

We thank the Psychiatric Institute 'Dr. José Horwitz B.' personnel for their help in the study. This study was in part funded by Pontificia Universidad Católica de Chile and Universidad Finis Terrae.

REFERENCES

1. Melle I, Larsen TK, Haahr U *et al*. Reducing the duration of untreated first-episode psychosis: effects on clinical presentation. *Arch Gen Psychiatry* 2004; **61:** 143–50.
2. Chong S-A, Mythily S, Verma S. Reducing the duration of untreated psychosis and changing help-seeking behaviour in Singapore. *Soc Psychiatry Psychiatr Epidemiol* 2005; **40:** 619–21.
3. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry* 2005; **62:** 975–83.
4. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry* 2005; **162:** 1785–804.
5. Penttilä M, Jääskeläinen E, Hirvonen N, Isohanni M, Miettunen J. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* 2014; **205:** 88–94.
6. Melle I, Johannesen JO, Friis S *et al*. Early detection of the first episode of schizophrenia and suicidal behavior. *Am J Psychiatry* 2006; **163:** 800–4.
7. Hegelstad WT, Larsen TK, Auestad B *et al*. Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome. *Am J Psychiatry* 2012; **169:** 374–80.
8. Bertolote J, McGorry P. Early intervention and recovery for young people with early psychosis: consensus statement. *Br J Psychiatry* 2005; **187** (Suppl. 5)**:** 116–9.
9. Patel V, Kim Y. Contribution of low- and middle-income countries to research published in leading general psychiatry journals, 2002–2004. *Br J Psychiatry* 2006; **190:** 77–8.

10. American Psychiatric Associations. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Washington: American Psychiatric Association, 2011.
11. Ministry of Health, Chile. *Guías Clínicas para el tratamiento de personas con un primer episodio de Esquizofrenia*. Santiago: Chile, 2009.
12. Perkins DO, Leserman J, Jarskog LF, Graham K, Kazmer J, Lieberman JA. Characterizing and dating the onset of symptoms in psychotic illness: the Symptom Onset in Schizophrenia (SOS) inventory. *Schizophr Res* 2000; **44:** 1–10.
13. Kay SR, Opler LA, Fiszbein A. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13:** 261–76.
14. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the Positive and Negative Syndrome Scale for schizophrenia. *Psychiatr Res* 1988; **23:** 99–110.
15. Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry* 2005; **162:** 441–9.
16. Cotton SM, Lambert M, Schimmelmann BG *et al*. Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis. *Schizophr Res* 2009; **114:** 17–24.
17. Lambert M, Conus P, Lubman DI *et al*. The impact of substance use disorders on clinical outcome in 643 patients with first-episode psychosis. *Acta Psychiatr Scand* 2005; **112:** 141–8.
18. Jeppesen P, Petersen L, Thorup A *et al*. The association between pre-morbid adjustment, duration of untreated psychosis and outcome in first-episode psychosis. *Psychol Med* 2008; **38:** 1157–66.
19. Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr Bull* 1982; **8:** 470–84.
20. Rabinowitz J, Levine SZ, Brill N, Bromet EJ. The Premorbid Adjustment Scale structured interview (PAS-SI): preliminary findings. *Schizophr Res* 2007; **90:** 255–7.
21. Kirkpatrick B, Fenton W, Carpenter W *et al*. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull* 2006; **32:** 214–9.
22. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* 1970; **212:** 11–9.
23. Boonstra N, Klaassen R, Sytema S *et al*. Duration of untreated psychosis and negative symptoms–a systematic review and meta-analysis of individual patient data. *Schizophr Res* 2012; **142:** 12–9.
24. Larsen TK, Melle I, Auestad B *et al*. Early detection of first-episode psychosis: the effect on 1-year outcome. *Schizophr Bull* 2006; **32:** 758–64.
25. Kahn RS, Fleischhacker WW, Boter H *et al*. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet* 2008; **371:** 1085–97.
26. Schennach-Wolff R, Seemüller FH, Mayr A *et al*. An early improvement threshold to predict response and remission in first-episode schizophrenia. *Br J Psychiatry* 2010; **196:** 460–6.
27. Gallego JA, Robinson DG, Sevy SM *et al*. Time to treatment response in first-episode schizophrenia: should acute treatment trials last several months? *J Clin Psychiatry* 2011; **72:** 1691–6.
28. Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. *Acta Psychiatr Scand Suppl* 2000; **401:** 3–38.
29. Pompili M1, Lester D, Dominici G *et al*. Indications for electroconvulsive treatment in schizophrenia: a systematic review. *Schizophr Res* 2013; **146:** 1–9.
30. Zervas IM, Theleritis C, Soldatos CR. Using ECT in schizophrenia: a review from a clinical perspective. *World J Biol Psychiatry* 2012; **13:** 96–105.
31. Robinson DG, Schooler NR, John M *et al*. Medication prescription practices for the treatment of first episode schizophrenia-spectrum disorders: data from the national RAISE-ETP study. *Am J Psychiatry* 2015; **172:** 237–48.
32. Turner D, Van der Gaag M, Karyotaki E, Cuijpers P. Psychological interventions for psychosis: a meta-analysis of comparative outcome studies. *Am J Psychiatry* 2014; **171:** 523–38.