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ORIGINAL PAPER

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Predictors of response in a sample of treatment-resistant psychotic patients on clozapine

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Abstract This study aims at identifying potential predictors of clinical response and functional outcome in 101 neuroleptic-refractory patients with a DSM-III-R diagnosis of schizophrenia (N = 34), schizoaffective disorder (N = 30) or bipolar disorder with psychotic features (N = 37), naturalistically treated with clozapine over a 48-month period. The "clinical response" and "functional outcome" criteria were respectively defined *a priori* as: a reduction of at least 50 % in the Brief Psychiatric Rating Scale total score in one evaluation with respect to baseline; and a Global Assessment of Functioning Scale score of at least 50. Several clinical and socio-demographic variables were assessed at baseline and only the diagnosis of bipolar disorder was significantly related with the clinical response. Variables significantly related with the functional outcome were female gender, university education and early age at onset.

Key words clozapine · schizophrenia · schizoaffective disorder · psychotic bipolar disorder · predictor of response

Introduction

Clozapine is well established for the treatment of psychotic patients, either schizophrenics, bipolars or schizoaffectives, also when refractory and/or intolerant to conventional antipsychotics [4, 7–9, 14, 19, 28, 29, 33]. Several studies [6, 11, 15, 16, 18, 23] have investigated possible predictors of response in patients on clozapine, reporting a favourable role of: paranoid schizophrenia subtype [11, 15], male gender [15], later age at onset [15, 23], shorter duration of illness [15], higher levels of positive [20, 24, 30] and lower levels of negative symptoms [11, 30]. Limits of these studies were: small sample sizes and short terms of observation. The latter enabled to include patients who might have met the response criterion after several months, in fact our previous study on patients on clozapine reported a time course to response on average 3 months for bipolars, 6 months for schizoaffectives and 24 months for schizophrenics [9].

The present study is aimed at identifying the potential predictors of clinical response and functional outcome in a sample of 101 neuroleptic-refractory psychotic patients who were assigned to a naturalistic, open-label, long-term (48 months) clozapine study.

Method

Study sample

A total of 101 treatment-resistant psychotic patients were consecutively recruited for a clozapine naturalistic follow-up program at the day-hospital service and wards of the Department of Psychiatry, University of Pisa, Italy. The sample and method of this follow-up study are described in detail elsewhere [9]. Patients presented a diagnosis of schizophrenia (N = 34), schizoaffective disorder (N = 30) or bipolar disorder with psychotic features (N = 37), according to DSM-III-R [1]. Fifty-four patients (58.8 % of schizophrenics, 36.7 % of schizoaffectives, and 62.2 % of psychotic bipolars) discontinued the treatment with clozapine during the 48-month follow-up period. Reasons for discontinuation and clozapine dosages are described in detail elsewhere [9]. In addition to clozapine patients were administered: typical neuroleptics (42.6 %), anticonvulsants (22.8 %), antidepressants (47.5 %), benzodiazepines (12.9 %) and lithium (11.9 %). Patients received doses of concomitant neuroleptic therapy no greater than the equivalent of 150 mg/day of chlorpromazine. Compliance to clozapine was investigated during clinical assessment through direct question to patients and accompanying relatives.

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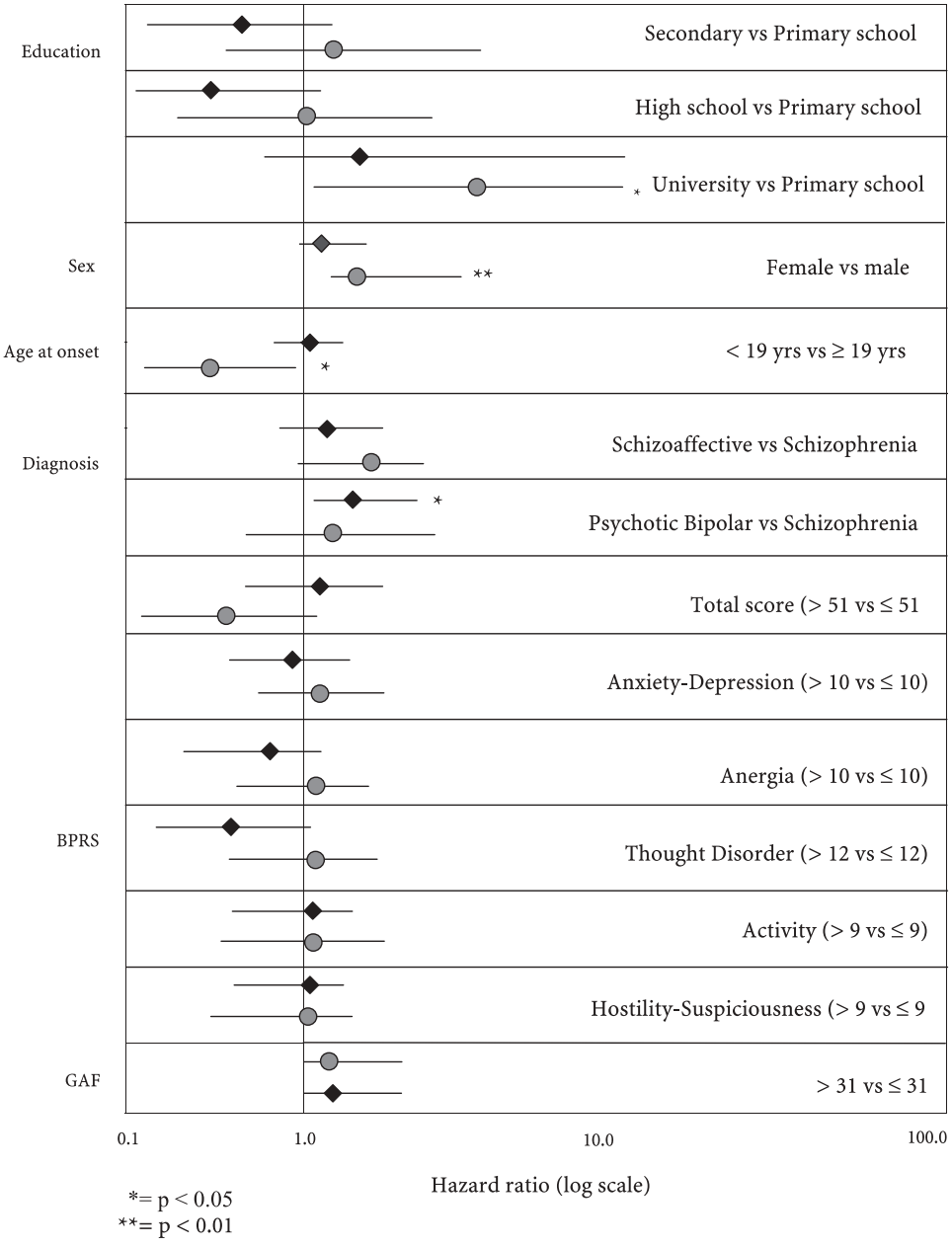

Fig. 1 Hazard ratios (diamonds) for achieving the clinical response criterion, hazard ratios (grey spots) for achieving the functional outcome criterion and 95% confidence intervals (whiskers), from cox regression final model, associated with different characteristics of 101 patients treated with clozapine

Assessment of patients' characteristics

Severity of psychopathology was assessed at baseline and after 1, 3, 6, 12, 18, 24, 36 and 48 months by using the 18-item Brief Psychiatric Rating Scale (BPRS) [21] on a 0–6 scoring scale. "Clinical response" criterion was defined *a priori* as a reduction of at least 50% in BPRS total score in one evaluation with respect to baseline.

Psycho-social and occupational functioning was measured by using the Global Assessment of Functioning Scale (GAF) [13] referred to the previous year. GAF scale was administered at baseline and after 12, 24, 36 and 48 months of treatment or at the discontinuation. The criterion for "functional outcome" was defined *a priori* as a GAF score of at least 50.

Sixteen clinical and socio-demographic variables, collected at baseline, were evaluated as potential predictors of clinical response and functional outcome (continuous variables were dichotomised based on the sample median): family history for psychiatric disorder, employment (unemployed, worker, office-worker, student, retired or housewife), marital status (single, married or divorced), current age (≤ 32 or > 32), treatment with clozapine monotherapy or with a combination of clozapine and other drugs, education (primary school, secondary school, high school, university), gender, diagnosis (schizophrenia, schizoaffective or bipolar disorder), age at onset (≤ 19 or > 19 yrs), GAF total score (≤ 31 or > 31), BPRS total score (≤ 51 or > 51) and its 5 factors' score (Anxiety-Depression ≤ 10 or > 10; Anergia ≤ 10 or > 10; Thought disorder ≤ 12 or > 12; Activity ≤ 9 or > 9; Hostility-Suspiciousness ≤ 9 or > 9).

Statistical analysis

Patients' baseline characteristics were compared across diagnoses by exact tests (categorical variables) and non-parametric tests (continuous variables). Cox multivariate regressions [10] were then applied to model time to clinical response and time to functional outcome, separately. At first, all the recorded patient's characteristics were included as independent variables. Then, only the eleven significant (p-value < 0.05) predictors and confounders were kept in the final models pre-

sented in the present paper: education, gender, diagnosis, age at onset, GAF score and BPRS total and its 5 factors' score. All the pairwise interaction terms were nonsignificant and left out of the final model.

Results

The clinical and socio-demographic variables considered were introduced into a Cox regression model in order to detect their association with the clinical response (see Fig. 1). Among these variables, only the diagnosis of bipolar disorder was significant when compared to schizophrenia, with bipolars being more likely to respond (p-value < 0.05). The following variables tended to be favourably associated with the clinical response even though not statistically significant: schizoaffectives vs schizophrenics; university graduated patients vs primary educated; females; higher BPRS and GAF total scores; and lower BPRS Thought Disorder and Anergia factor scores.

The eleven variables considered were introduced into a Cox regression model in order to detect their association with the functional outcome (see Fig. 1). Females ($p < 0.01$), graduated patients vs primary educated ($p < 0.05$), and patients with early age at onset ($p < 0.05$) were significantly more likely to achieve the functional outcome. The following variables tended to be favourably associated with the functional outcome even though not statistically significant: bipolars and schizoaffectives vs schizophrenics, higher GAF scores, lower BPRS total scores and higher scores in BPRS Anxiety-Depression, Anergia, Thought Disorder and Activity factors.

Discussion

In the present study, bipolar and schizoaffective patients were more likely to meet the clinical response and functional outcome criteria than schizophrenic patients, although the association was significant only for bipolar patients with respect to the clinical response. These findings are consistent with previous studies reporting greater clozapine efficacy in the treatment of affective psychosis [8, 19, 32] than of schizophrenia.

Our results showed female gender to be more likely to meet the functional outcome criterion besides later age at onset. Previous results on gender differences are not consistent: some authors found a poorer response to antipsychotic drugs in schizophrenic men [2, 25, 26, 29], whereas others found female gender to be predictor of poor response to clozapine treatment [15, 16].

According to previous studies [5, 15–17, 31], higher baseline level of psychosocial and occupational functioning and university education correlated positively with the clinical response and the functional outcome, significance was only detected between functional outcome and university education.

A more severe baseline global psychopathology was positively associated with the clinical response, consistent with previous findings [20, 24, 30], and negatively associated with the functional outcome. In the present report poorer clinical response was associated with higher BPRS Anergia factor scores, in line with other studies [11, 30], and with higher BPRS Thought Disorder factor scores, in contrast with other studies [20]. The functional response was favourably but not significantly associated with higher scores in four BPRS factors (Anxiety-Depression, Anergia, Thought Disorder and Activity). These findings require further studies, also considering that other authors suggested the presence of the same symptomatology, present across different diagnoses, that might define subpopulations of importance for targeted therapies [27].

Unfortunately, the open design of this study does not allow us to distinguish to what extent the predictors of response identified are related to clozapine treatment and to other variables, such as the natural course of illness, particularly among bipolar, schizoaffective and schizophrenic patients and additional drugs to clozapine. Also, the relatively small sample size hindered the possibility of considering the joint effect of the several variables available in large multivariate models. Despite the long-term follow-up, much longer than the majority of similar studies reported in the literature, the present study presented higher rates of compliance than previous clozapine studies comparable for length of observation [3, 9, 12].

Further randomised double-blind, placebo-controlled studies are necessary to better estimate the role of the predictive factors identified by the present report in determining the response to clozapine.

References

1. American Psychiatric Association (1987) Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, D.C.: American Psychiatric Association
2. Angermeyer MC, Kuhn L, Goldstein JM (1990) Gender and the course of schizophrenia: differences in treated outcomes. Schizophr Bull 16(2):293–307
3. Banov MD, Zarate CA, Tohen M, Scialabba D, Wines JD, Kolbrener M, Kim JW, Cole JO (1994) Clozapine therapy in refractory affective disorders: polarity predicts response in long-term follow-up. J Clin Psychiatry 55(7):295–300
4. Battegay R, Cotar B, Fleischhauer J, Rauchfleisch U (1977) Result and side effects of treatment with clozapine (Leponex R). Compr Psychiatry 18:423–438
5. Bottlender R, Sato T, Jager M, Groll C, Srauss A, Moller HJ (2002) The impact of duration of untreated psychosis and premorbid functioning on outcome of first inpatient treatment in schizophrenic and schizoaffective patients. Eur Arch Psychiatry Clin Neurosci 252 (5):226–231
6. Buchanan RW, Breier A, Kirkpatrick B, Ball P, Carpenter WT Jr (1998) Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. Am J Psychiatry 155:751–760
7. Calabrese JR, Kimmel SE, Woyshville MJ, Rapport DJ, Faust CJ, Thompson PA, Meltzer HY (1996) Clozapine for treatment-refractory mania. Am J Psychiatry 153:759–764
8. Cassano GB, Ciapparelli A, Villa M (1997) Clozapine as a treatment tool: only in resistant schizophrenic patients? Eur Psychiatry 12 (suppl 5):347–351

9. Ciapparelli A, Dell'Osso L, Bandettini di Poggio A, Carmassi C, Cecconi D, Fenzi M, Chiavacci MC, Bottai M, Ramacciotti C, Cassano GB (2003) Clozapine in treatment-resistant patients with schizophrenia, schizoaffective, and psychotic bipolar disorder: a naturalistic 48-month follow-up study. J Clin Psychiatry 64: 451–458
10. Cox DR (1972) Regression models and life tables (with discussion). J Royal Statistical Society Ser B 34:187–220
11. Fanton WS, Lee B (1993) Can clozapine response be predicted? A naturalistic pilot study. J Nerv Ment Dis 181(1):62–64
12. Gitlin MJ, Swendsen J, Heller TL, Hammen C (1995) Relapse and impairment in bipolar disorder. Am J Psychiatry 152:1635–1640
13. Jones SH, Thormicroft G, Coffey M, Dunn G (1995) A brief mental health outcome scale. Reliability and validity of the Global Assessment of Functioning (GAF). Br J Pychiatry 166:654
14. Kane JM, Honigfeld G, Singer J, Meltzer H (1988) Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45:789–796
15. Lieberman J, Kane JM, Safferman AZ, Pollack S, Howard A, Szymanski S, Masiar SJ, Kronig MH, Cooper T, Novacenko H (1994 a) Predictor of response to clozapine. J Clin Psychiatry 55 (suppl B)9:126128
16. Lieberman JA, Safferman AZ, Pollack S, Szymanski S, Johns C, Howard A, Kronig M, Bookstain P, Kane JM (1994 b) Clinical Effects of Clozapine in Chronic Schizophrenia: Response to treatment and predictor of outcome. Am J Psychiatry 151:1744–1752
17. Loebel AD, Lieberman JA, Alvir JM, Mayerhoff DI, Geisler SH, Szymanski SR (1992) Duration of psychosis and outcome in first-episode schizophrenia. Am J Psychiatry 149(9):1183–1188
18. Marder S, Van Putten T (1988) Who should receive clozapine? Arch Gen Psychiatry 45:865–876
19. McElroy SL, Dessain EC, Pope HG, Cole JO, Keck PE Jr, Frankenberg FR, Aizley HG, O'Brien S (1991) Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. J Clin Psychiatry 52:411–414
20. Meltzer HY, Bastani B, Young Known K, Ramirez LF, Burnett S, Sharpe J (1989) A prospective study of clozapine in treatment-resistent schizophrenic patients. Psychopharmacology 99 (suppl):S68–S72
21. Overall JE, Gorham DR (1962) The Brief Psychiatric Rating Scale. Psychol Rep 10:799–812
22. Pickar D, Owen RR, Litman RE, Konicki PE, Gutierrez R, Rapaport MH (1992) Clinical and Biologic Response to Clozapine in patients with Schizophrenia. Arch Gen Psychiatry 9:345–352
23. Pickar D, Owen RR, Litman RE, Hsiao JK, Su TP (1994) Predictors of Clozapine Response in Schizophrenia. J Clin Psychiatry 55:129–132
24. Rosenheck R, Lawson W, Cryton J Cramer J, Xu W, Thomas J, Stolar M, Charney D (1998) Predictors of differential response to clozapine and haloperidol. Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. Biol Psychiatry 44:475–482
25. Seeman MV (1982) Gender differences in schizophrenia. Can J Psychiatry 27(2):107–112
26. Seeman MV (1986) Current outcome in schizophrenia: women vs men. Acta Psychiatr Scand 73:609–617
27. Serretti A, Rietschel M, Lattuada E, Krauss H, Schultze TG, Muller DJ, Maier W, Smeraldi E (2001) Major psychoses symptomatology; factor analysis of 2241 psychotic subjects. Eur Arch Psychiatry Clin Neurosci 251 (4):193–198
28. Suppes T, Webb A, Paul B (1999) Clinical outcome in 1-year trial of clozapine versus treatment as usual for patients with treatment-resistent illness and history of mania. Am J Psychiatry 156: 1164–1169
29. Szymanski S, Lieberman JA, Alvir JM, Mayerhoff D, Loebel A, Geisler S, Chakos M, Koreen A, Jody D, Kane J (1995) Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. Am J Psychiatry 152(5):698–703
30. Umbricht DS, Wirshing WC, Wirshing DA, McMeniman M, Schooler NR, Marder SR, Kane JM (2002) Clinical predictors of response to clozapine treatment in ambulatory patients with schizophrenia. J Clin Psychiatry 63:420–424
31. Wyatt RJ (1991) Neuroleptics and the natural course of schizophrenia. Schizophr Bull 17(2):325–351
32. Young CR, Longhurst JG, Bowers MB, Mazure CM (1997) The expanding indications for clozapine. Exp and Clin Psychopharmacol 5(3):216–234
33. Zarate CA, Tohen M, Banov M, Weiss MK, Cole JO (1995) Is clozapine a mood stabilizer? J Clin Psychiatry 56:108–112