Relapsing versus non relapsing course of schizophrenia: a cohort study in a community based mental health service

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SUMMARY. **Aim** – We examined the effect of several clinical variables on the tendency to relapse and to require hospitalization in a cohort of patients, living in the community and followed up naturalistically for seven years. **Method** – Forty-six patients affected by schizophrenia and schizoaffective disorder, according to both DSM-IV and ICD-10 criteria, were assessed by Positive and Negative Syndrome Scale and Life Skills Profile (LSP). All patients consecutively enrolled, were assessed in a stable clinical phase of illness and treated as usual by their reference psychiatrist. Social and clinical outcome was assessed yearly for seven years after the study entry and analyzed with survival analysis. **Results** – Patients who did not relapse, were characterized by higher functioning, lower positive symptoms, higher ability in self-care and non-turbulence and higher IQ at their baseline clinical evaluation. These variables were entered in a Cox regression model to corroborate the predictive power on the relapsing course of illness. Only IQ and non-turbulence scores of LSP were entered in the equation (Wald method: p=0.007 and p=0.002 respectively). **Conclusions** – Several factors interact with the course of illness and influence the tendency to require hospitalization. In the present study we report that non-turbulence is a significant predictor of a non-relapsing course of illness. Further studies are needed to clarify the role of other mediating variables.

Declaration of Interest: none.

KEY WORDS: schizophrenia, hospitalization, outcome, community psychiatry.

INTRODUCTION

Schizophrenia still remains a severe, disabling and costly disease for the individuals affected, their families and for mental health services (Knapp et al., 2004). The outcome is heterogeneous, the prognosis appears devastating for about 25% and poor, with an undulating course, for half of the patients (Modestin et al., 2003).

Therefore, predicting the prognostic trajectories of the disease at the individual level, is a critical point for implementing proper interventions and optimizing the resources of mental health services.

Several predictors have been identified, but a large portion of general variance of outcome remains unexplained. Among others: illness characteristics (Dickerson et al.,

1996; Norman et al., 1999), environment (Butzlaff & Hooley, 1998), correct and effective treatment options, mental health services orientation and commitment (Ruggeri et al., 2003), compliance to intervention (Gaebel, 2004) and treatment and social support (Harding & Keller, 1998; Bromet & Fennig, 1999) should be remembered.

Relapses and hospitalizations are outcome measures widely used in clinical research even though they are not strongly associated with symptom severity and prognosis (Mueser et al., 1998). Additional indicators of outcome are: satisfaction with daily occupations and quality of life (Eklund et al., 2001), the number of beds available in the area and the possibility to refer the patient discharged from hospital to community care for further care (Sytema et al., 2002).

It should be noted, in fact, that Wykes et al. (1998) provided evidence that intensive community services are able to reduce hospital admission, even though the impact in measures of disability and symptoms is negligible.

Whatever the outcome, assessed in terms of relapses and/or re-hospitalization, it is a largely unexplored issue in countries where mental health services are strongly committed to community care.

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In the present naturalistic study, we compared socio-demographic, clinical and cognitive characteristics of patients who were admitted to a psychiatric unit for clinical exacerbation (defined as relapsed) vs. patients who did not relapse in a span period of seven years of follow up, in order to look for possible predictive variables of outcome.

The aims of the present study were manifold:

1. Does the baseline clinical profile overlap between relapsing vs. non-relapsing patients?
2. Which variables, assessed at baseline, have significant power to predict the first hospitalization which occurred after study entry?
3. Is relapse a reliable and valid indicator of poor outcome in patients living in communities where case management is incorporated into the routine practice of mental health services?

METHOD

The present study describes a follow-up comprehensive assessment of a cohort of schizophrenia subjects consecutively enrolled from the 2nd January 1998 (Di Michele *et al.*, 2001; Di Michele & Bolino, 2004) who were invited to take part to this naturalistic study. The study was conducted in a community based mental health service (Pescara Mental Health Center) of the Department of Mental Health of Pescara (Italy).

The procedure of the study conformed to the standards of the Local Health Agency ethical committee. In short, the sample was unselected and enrolled in a quasi-random modality.

The study was restricted to fifty subjects who fulfilled the study criteria for several reasons: economical restraints, the psychologist (for neuropsychological testing) and a skilled collaborating nurse (for function assessment) were available for a limited span period, the Life Skills Profile copyright was available for a limited sample. Moreover, a detailed and comprehensive clinical, cognitive, socio-demographic assessment, with clinical contact on a monthly basis did not allow the recruitment of a sample of a larger size. All patients were followed up for seven years and all of them, apart from five patients who dropped out because of death, are currently under treatment and assessment procedures.

Subjects

Fifty schizophrenic patients accurately diagnosed according to the DSM-VI (American Psychiatric Association,

1994) and ICD-10 (World Health Organization, 1992) participated in the study. Three patients later refused to take part in the study, one patient did not fulfill criteria for study entry (cannabis user). The remaining forty-six provided a formal agreement and written informed consent. Because of the naturalistic and pragmatic design of the study inclusion criteria were: age > 18 years old and personal consent to participate. Exclusion criteria were: head injury with loss of consciousness for more than 30 minutes and concurrent diagnosis of epilepsy. Drug abuse (Cannabis, heroin and cocaine) was also an exclusion criterion.

Co-morbidity was mainly with tobacco smoking and alcohol misuse.

Patients were treated by their reference psychiatrist as usual and were on maintenance doses of typical and atypical antipsychotic medication. Neuroleptic dosage was converted into Chlorpromazine equivalent (Eq/CPLZ) (Lehman, 1998).

The baseline clinical, cognitive and functional assessment was made after clinical stabilization of patients and the absence of relapse or symptom recurrence or exacerbation in a time period near the baseline assessment was also corroborated for patients potentially eligible.

Detailed clinical records are available for each patient. The study is still continuing according to the protocol and patients who have survived are currently under treatment by their reference psychiatrist. Patients who are currently hospitalized in residential facilities are subjected to recurrent visits by their case management staff.

Procedures

Assessment with the following instruments was made at baseline.

Positive and Negative Symptom Score Scale (PANSS) was used to assess positive and negative symptoms (Kay *et al.*, 1986).

Clinical Global Impression Scale (Guy, 1976) was used for assessment of severity of illness.

Life Skills Profile (LSP) (Rosen *et al.*, 1989) was used to measure those aspects of functioning ("life skills") which affected how successfully people with schizophrenia lived in the community or hospital. The 39 item rating scale was used for the present study. LSP assesses five areas: self-care, non-turbulence, social contact, communication and responsibility and was designed for research in community focused services. High scores indicate high levels of life skills.

Global Assessment of Functioning (GAF) was also used for general assessment of social function (American Psychiatric Association, 1994).

Raven's Progressive Matrices (Raven, 1984) was administered at baseline by a clinical psychologist to assess the visuo-spatial intellectual level.

For the present study the major endpoint was the first hospital admission (voluntary and compulsory) which occurred over the span of 7 years. This defined a patient as a relapser.

Surrogate endpoints that are part of the general design of the study were: living arrangements (residential facility or independent living) employment (sheltered /not sheltered), occurrence of any alcohol related diagnosis (ARD), evaluation of psychosocial and pharmacological treatment adherence. In the present study an independent rater (FB), blindly evaluated all patients and their clinical records for endpoint variables.

Patients were rated as non-adherent if they had stopped pharmacological and psychosocial therapy at least twice in the year which preceded the baseline assessment and this was currently controlled during the follow up evaluation. Direct interviews with the patients and caregivers, and evaluation of clinical records were conducted.

The ascertainment of major and surrogate endpoint variables in the long term was made through the following sources: analysis of clinical records, direct interview with patients or relatives and/or the Case Manager, analysis of the Psychiatric Hospitalization Case Registry of the catchment area. Alcohol Related Diagnosis (ARD) was ascertained if any of the following emerged: recourse to an emergency unit for alcohol misuse, any clinical and laboratory evidence of alcohol dependence and/or abuse.

Statistical analysis

Comparisons of baseline characteristics between the two outcome groups (relapser vs non relapser) included chi-square tests for categorical variables and t-test for continuous variables. Chi-square test was used for 2 by 2 table. Comparisons of baseline characteristics between the two groups were carried out using Chi-square test (or Fisher's Exact test if any frequency was <5) for categorical variables and t-test for continuous variables.

Cox Proportional Hazard-Regression Analysis and Kaplan-Meier estimates were also used. Both tests were used for looking at the interval between two events and are based on the assumption that the second event (e.g. relapse) does not necessarily happen to everyone and when people are followed for different periods of time. A Kaplan Meier survival analysis was subsequently conducted. This method is a nonparametric (actuarial) technique for estimating time-related events.

The test of null hypothesis that survival distribution is the same for the subgroups, was calculated with Wilcoxon (Gehan) test and post hoc Breslow test.

All statistical tests were two-tailed at an alpha level of 0.05. Bonferroni correction for multiple comparison was not calculated, in these cases a p value<0,01 should be considered more appropriate.

SPSS-12 version was used for statistical analysis.

RESULTS

The sample mean age was 39.7 (s.d. 9.0), the mean years of education were 10.8 (s.d. 3.6) and the mean duration of illness was 12.5 (s.d. 7.9); the mean age at onset was 27.2 (s.d. 6.2). The average dose of neuroleptic drugs was 602 mg Eq/CPLZ.

Males made up 56.5% of the sample.

1. The analysis of the baseline clinical profile between relapsing vs. non-relapsing patients

The whole sample was divided into two groups: relapsers (30 patients) vs. non-relapsers (16 patients). A Relapser was defined as a person with at least one hospital admission to an acute psychiatric unit (on a voluntary or compulsory basis).

Demographic and clinical variables for both groups are shown in table I. Due to the fact that Bonferroni correction was not calculated p level between 0.05 and 0.01 should be considered with caution.

Socio-demographic features. Relapser patients were indistinguishable from non-relapsers regarding gender, age, age at first contact and years of education. The age at first contact is remarkably older in both sub-samples (27.7 vs. 26.4). A possible explanation is that psychotic patients come into contact with mental health public services relatively late in the catchment areas where the study was conducted, suggesting thus a failure of services to treat disease at the early and "real" onset of schizophrenic symptoms, and that probably a significant delay occurs, with possible further negative implications on outcome.

Clinical features. Interestingly, relapser patients showed more severe positive symptoms at study entry, thus suggesting a possible marker of a higher severity of illness in patients attending mental health services.

In addition, the analysis of *function variables* add further arguments to the view that "disruptive" characteristics of illness are more frequent in this type of clinical population. Of great interest is the finding of more seve-

re *intellectual impairment* in relapser patients, documenting that relapsers, as a whole, are characterized by disability, symptomatic and cognitive difficulties when compared with non-relapser patients.

GAF score approached statistical significance. Raven (t=2.3), self-care (t=2.4), non-turbulence (t=2.3) and PANSS positive symptom scores (t=2.9) differed significantly between groups.

Table I. – *Baseline Demographic and clinical variables in relapser vs. non relapser group. Mean (SD).*

	RELAPSER (30)	NON RELAPSER (16)	p
Male*	63.3%	43.7%	NS
Age	40.4 (9.6)	38.3 (8.0)	NS
Years of education	10.6 (3.6)	11.1 (3.6)	NS
Age at first contact	27.7 (6.7)	26.4 (5.3)	NS
Global Clinical Impression	6 (1.0)	5.4 (1.0)	NS
PANSS-Positive	24.4 (8.4)	19 (3.9)	0.005
PANSS-Negative	25.1 (9.4)	22.3 (9.1)	NS
PANSS-Global psychopathology	44.8 (9.1)	42.5 (9.0)	NS
PANSS Total score	94.1 (22.5)	83.8 (19.2)	NS
Extra-pyramidal symptom score	5.2 (4.6)	4 (2.1)	NS
GAF	44.2 (15.4)	53.8 (15.9)	NS
LSP "self-care"	26.7 (8.1)	31.2 (4.3)	0.019
LSP "non turbulence"	41.2 (6.9)	45.1 (3.3)	0.023
LSP "social contact"	11.4 (3.1)	11.4 (3.2)	NS
LSP "communication"	18.8 (3.9)	17.8 (3.8)	NS
LSP "responsibility"	16 (3.9)	17.6 (1.5)	NS
LSP total score	116.2 (20.4)	123.4 (12.3)	NS
Raven progressive matrices score	22.6 (10.4)	28.3 (4.2)	0.025

T.test was used for all comparisons; * Chi-squared test.

2. Analysis of the predictive power of variables

Baseline score of Raven test, self care, non turbulence and PANSS positive symptom score were entered in a Cox proportional Hazard-Regression model to verify the predictive power of several factors on the relapsing course of illness (Time to first admission was entered as dependent variable). Raven and non-turbulence scores only were entered in the equation (Wald method: p=0.007 and p=0.002, respectively). The analysis suggest that non verbal IQ and misconduct are predictors of relapse and hospital admission.

The intent was to compare survival functions of relapsers vs. non-relapsers with the purpose of quantifying the "power" of predictors to anticipate or prolong time to first admission.

To do this, non-turbulence score and Raven score were dichotomized in low vs. high score group based on the median value. The comparison of the low vs. high score group yielded statistically significant differences on the Kaplan Meier estimate for non-turbulence score (Breslow test, p=0.0187) only (figure 1). In other words, the time to first hospitalization after study entry, in patients cha-

racterized by low turbulent behaviour, was twice the median time of turbulent people (56 vs. 25 months; (C.I. 19.3-30.6 vs 43.6-68.3, respectively). Because of a gender effect related to conduct disorder (Robins & Price, 1991; Arsenault *et al.*, 2000) which is encompassed by the concept of turbulence, a further chi-square test was calculated. According to literature data and to our prediction, a gender effect is reported (Chi-square test p=0.025), there being more males than females displaying "turbulent" behaviour. However, this effect did not influence outcome and gender did not predict outcome (Chi-square test, NS).

3. The analysis of relapses as indicators of poor outcome patients living in communities where case management is incorporated into the routine of mental health services

In order to answer this basic question several analysis were carried out. Continuous variables were dichotomized where needed for entering the statistical analysis.

Comparisons showed that relapser patients are admitted to long term residential rehabilitation facilities with
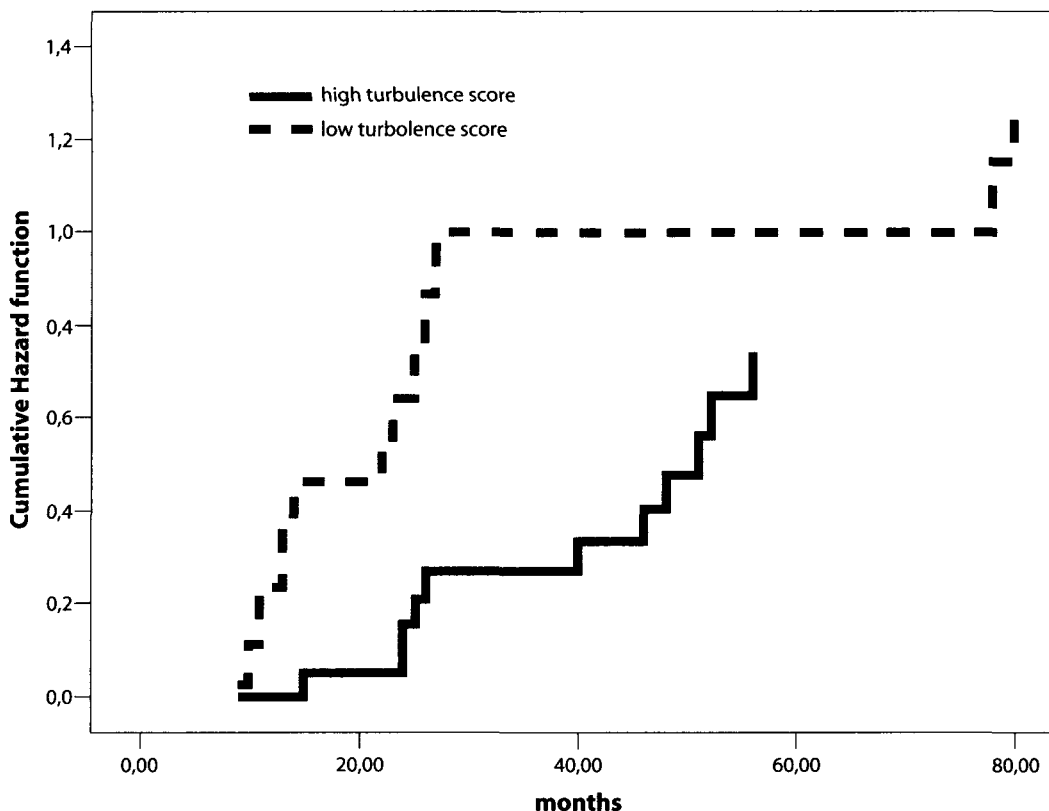
Figure 1 – *Hazard Function of time to relapse in patients with low vs. high turbulence score.*

significantly higher frequency (26.8% vs 4.9%). In addition, they needed more frequent compulsory admission, had poorer psychosocial functioning, were considered not compliant according to the operational criteria of the study and an alcohol related diagnosis was formulated more often. Results are depicted in table II.

Table II. – *Variables associated with the status of relapsing or not relapsing (Pearson chi square or Fisher's exact test if appropriate, two-sided test, p<0.05).*

	relapser	non-relapser	p
Residential rehabilitation*			
Residential facility	26.8%	4.9%	**0.045**
Never Residential facility	34.1%	34.1%	
Compulsory admission			
At least once	26.1%	0%	**0.003**
Never	39.1%	34.8%	
Psychosocial functioning at baseline (median value as cut-off)			
Low global functioning	43.5%	10.9%	0.022
High global functioning	21.7%	23.9%	
Adherence to comprehensive treatment at baseline			
Compliant patients	34.8%	34.8%	**0.001**
Non compliant patients	30.4%	0%	
Addiction			
Alcohol misuse	17.4%	0%	**0.037**
No alcohol misuse	47.8%	34.8%	

5 out 46 patients were deceased; ** analysis conducted on 36 patients

DISCUSSION

The present study included outcome variables strictly related to hospital and residential service utilization, and provided data potentially useful for proper planning of health care service organizations and direct evaluation of costs. A previous epidemiological cohort study (Gaddini *et al.*, 2005), using administrative data, reported a very high rate of hospital readmission in a cohort of patients collected at their first psychiatric admission and followed up for 4 years. In this study the authors provided evidence that risk of readmission appeared to be related to the level of integration with mental health community facilities.

We found out that, in a community cohort of schizophrenic people treated naturalistically by mental health services and who received comprehensive treatment in settings that prioritised the continuity of care, predictors of re-hospitalization may be identified and may be used for planning appropriate services. Our findings are limited by the small sample size, however, we believe that appropriate planning of interventions may be implemented in order to reduce hospitalization, and to postpone the resorting to long term residential facilities in the final stages of the disease. The findings of the study are discussed hereafter in more detail.

1. The baseline profile in relapsers vs. non-relapsers

Relapser patients differed from non-relapsers in a small set of baseline variables regarding psychopathology, function and intellectual functioning. Our conclusions are, however, weakened by the lack of Bonferroni correction for multiple comparison.

An average higher score of positive symptoms characterizes the relapser group. The prediction power of higher symptomatology was detected in a previous analysis of the present cohort, three years after the baseline assessment (Di Michele & Bolino, 2004) and is confirmed in the present study. This effect, however, is weak. In fact, positive symptom score did not enter as a significant predictor in the Cox Regression Hazard analysis.

This finding needs some comment, in the light of the inclusion criterion of the study in which a stabilization phase was needed before psychopathological and cognitive assessment. In fact, previous studies have cautioned against the inclusion in long-term outcome studies of patients assessed in an acute phase of illness (Norman *et al.*, 1999). This is most important for community based studies conducted in Italy where the strong commitment to community care has neglected care in hospital, and a disproportionate short stay characterizes the intervention

and treatment in acute psychiatric units that are located in general hospitals. This implicates the commitment to stabilize relapsing acute psychotic patients in the community instead of in inpatient units.

However, relapser patients show severe psychosocial disability evident from their lower score on GAF and LSP subscales *self-care*. Even though a strict interrelationship between function and symptoms has been questioned on clinical grounds, they may be described as equivalent phenomena.

The level of intellectual ability assessed by Raven test is lower in relapsing people. This confirms the view that patients with intellectual disability more likely show a poor outcome (Dickerson *et al.*, 1996) and that cognitive dysfunction may be an associated feature for defining a subgroup of schizophrenic people, able to live in the community, but at an increased risk of hospital admission.

2. Which variables are strongest predictors of relapse?

Cox Proportional Hazard-Regression Analysis yielded turbulence and low Raven score as the only significant predictors of the model between relapsers vs. non-relapsers. This suggests a general inadequacy of community based services to fulfil optimal treatment for social misconduct (Economou *et al.*, 2005). Moreover there is persuasive and empirical support that patients with severe mental illness present disrupted behaviour at a rate higher than that of the general population (Junginger & McGuire, 2004), and that the raised risk of violence is at least partially mediated by psychotic symptoms (Link *et al.*, 1992). In fact, delusions and hallucinations often account for a large part of this increased risk (Taylor *et al.*, 1998).

In addition there is a definite gender effect, widely reported in the literature, in which males are more frequently involved in violent and aggressive behaviour. This phenomenon has been described both in a hospital setting and in community based studies (Robins & Price, 1991). Several explanations have been suggested for the understanding of this phenomenon, but a consensus about the "biological" or "environmental" origins is far from being reached.

Disruptive behaviour is a significant reason for hospitalization as well. In fact, patients with a higher score on the LSP subscale assessing turbulent conduct are more likely to be admitted to a psychiatric ward at least once in the long-term following the baseline assessment. Interestingly, the score we reported in our sample of relapsers overlaps the score reported in patients living in Italian residential facilities (Zizolfi *et al.*, 2004), thus sug-

gesting that social misconduct and disrupted behaviour may influence clinical decisions for admitting people to residential long-term rehabilitation facilities in Italy. So we provide evidence that antisocial conduct is a significant predictor of admission to both acute psychiatric wards and rehabilitation residential facilities in a span period of seven years.

Some further comments need to be made about the use of LSP. This scale was developed recently, as a specific instrument in studies measuring disability in community based sample patients (Rosen *et al.*, 1989). We confirm evidence from the literature reporting a predictive capacity of LSP subscales (including non-turbulence) either contact with police, but also hospital readmission in schizophrenic patients (Parker & Hadzi-Pavlovic, 1995). It is interesting to notice that despite the remarkable difference between the sample and psychiatric services characteristics of Parker & Hadzi-Pavlovic (1995) and the present study conducted in a community sample with mental health services with a strong commitment to community treatment, the specific antisocial behaviours are able to predict outcome significantly and similarly.

Highly turbulent people stay out of hospital for a shorter time before admission, about half that of non-turbulent people (25 vs. 56 months). This supports the opinion that violent, aggressive and disrupted behaviour in general results from significant long-term unmet needs that pose major clinical problems needing specific supervision or care approaches (Kallert *et al.*, 2004). Examining the question on a different level of analysis, it is possible to argue that the toleration threshold for violent or antisocial behaviour is lower and admission is a primary option for starting or continuing optimal pharmacological treatment (Economou *et al.*, 2005) instead of, defend career and family members from potential aggressions and misconduct. Even though turbulence is a gender related effect, in the present sample gender did not significantly influence the percentage of relapsers vs. the percentage of non-relapsers.

In addition, we are aware of the important role played by conduct disorder in the outcome of schizophrenia and schizoaffective disorder and believe that "turbulence" is a target behaviour that influences the clinical approach to these patients. In fact, there is agreement that patients with antisocial behavioural features are younger at onset of psychoses, need more hospitalization and are vulnerable to substance misuse (Hodgins *et al.*, 2005).

The intellectual level is also lower in relapsers, but it is not related to time of relapse. This may be interpreted as a statistical artefact due to the lack of a post-hoc statistical control for multiple comparison. In fact, as can be noted in table II, when scores were dichotomized no differences emerged between groups. In addition, the small size of the group (36 patients) reduces the statistical power of the analysis. An average lower IQ score is suggestive of a more pronounced neuro dysfunction in relapsing people. Relapsers are more frequently rated as noncompliant in clinical records (table II). Two possible explanations are related to this finding: patients stop treatment because of an intolerance to side effects or, the lack of compliance is simply a feature associated with psychotic symptoms and turbulent behaviour (Junginger & McGuire, 2004). Alternatively such patients are less likely to be treated with assertive management by mental health services (Burns *et al.*, 2001). The association of alcohol misuse in relapsers contributes to identify a clinical subgroup characterized by pervasive clinical and psychosocial peculiarities. This suggests that conceptually, and not only speculatively, relapse is related to outcome (see also point 3 of the discussion section).

3. The relatedness of relapse with clinical outcome

We believe that in community settings the tendency to require hospitalization is a reliable and valid indicator of prognosis, settling a subgroup of patients with a definitely poor outcome. In addition, the operational definition of relapse has immediate and understandable implications also for administrative purposes and for planning improvement of quality of care in serious mental diseases.

Our analyses suggest that hospitalization is strictly related to outcome and prognosis and define a subgroup with a more severe form of illness. In fact, several factors pointing to poor prognosis are overrepresented in the relapser group (see also table II). Some important differences need to be further clarified. The percentage of patients with occasional alcohol misuse is higher in this group, thus suggesting a complex behavioural pattern in such a group. In addition, relapsers are less adherent to pharmacological intervention. Even though we used a fairly restrictive clinical operational criterion, it is worth noting that 16 patients of the relapser group were rated as noncompliant, whereas nobody was rated as noncompliant in the non-relapser group. This finding strongly supports the commitment to individualize as effectively as possible intervention at the individual level, possibly both with psychoeducation strategies and opting for "effective" psychopharmacological treatment. Conventional antipsychotic drugs are, on this ground, second line treatment options.

GENERAL CONCLUSION

Our findings report a disappointingly poor outcome for people affected by schizophrenia living in the community (Ruggeri *et al.*, 2004) and raise several clinical issues and challenges in terms of clinical intervention and health policy (Udechuku *et al.*, 2005): Should turbulent people, at the onset of disease, be treated with appropriate interventions, particularly when prominent cognitive dysfunction is associated? Should patients with aggressive and violent behaviour be treated in the same units as patients characterized by a more intimate and isolated mode of suffering? Should the residential rehabilitation facilities be considered equally effective and appropriate for violent and non violent persons, and (on the individual level), to what extent should personality and behavioural features be considered for proper or specific interventions?

Evidence from the literature clearly proves that community based services are partially ineffective for people with challenging behaviour and no advantage of a community based pattern of care has yet been demonstrated (Wikes *et al.*, 1998), so a possible issue may be related to the adequacy of the Italian Mental health system to provide for a specific clinical population or regarding the up-to-datedness of the Italian Psychiatric reform of 1978 (de Girolamo & Cozza, 2000). We are confident that the evaluation of misconduct and turbulent behaviour at the individual level should be a direct focus of pharmacological and psychosocial intervention in order to avoid or, to a lesser degree, to postpone hospitalization and/or admission to residential facilities.

Our findings suggest that many factors which are at work after the onset of psychosis as possible modifiers of the course, are significantly associated with course, outcome and tendency to relapse and/or to require hospitalization. Among others, misconduct and the inability to cope with peers and relatives are the strongest predictors of a negative outcome.

BIBLIOGRAFIA

American Psychiatric Association (1994). *Diagnostic and Statistical Manual for Mental Disorder*, 4th ed. American Psychiatric Association: Washington DC.

Arseneault L., Moffitt T.E., Caspi A. & Taylor P.J. & Silva P.A.(2000). Mental disorders and violence in a total birth cohort: results from the Dunedin Study. *Archives of General Psychiatry* 57, 979-986.

Bromet E.J. & Fennig S. (1999). Epidemiology and natural history of schizophrenia. *Biological Psychiatry* 46, 871-881.

Burns T., Fioritti A., Holloway F., Malm U. & Rossler W. (2001) Case management and assertive community treatment in Europe. *Psychiatric Services* 52, 631-636.

Butzlaff R.L. & Hooley J.M. (1998). Expressed emotion and psychiatric relapse: a meta-analysis. *Archives of General Psychiatry* 55, 547-552.

de Girolamo G. & Cozza M. (2000). The Italian psychiatric reform. A 20-year Perspective. *International Journal of Law and Psychiatry* 23(3-4), 197-214.

Dickerson F., Boronow J.J., Ringel N. & Parente F. (1996). Neurocognitive deficits and social functioning in outpatients with schizophrenia. *Schizophrenia Research* 21, 75-83.

Di Michele V. & Bolino F. (2004). The natural course of schizophrenia and psychopathological predictors of outcome - A community-based cohort study. *Psychopathology* 37(2), 98-104.

Di Michele V., Bolino F., Di Zio G. & Pincini P. (2001). Symptoms and social functioning features are aggregate in a tripartite structure. *Epidemiologia e Psichiatria Sociale* 10(3), 186-193.

Economou M., Palli A. & Falloon I. (2005). Violence, misconduct and schizophrenia: Outcome after four years of optimal treatment. *Clinical Practice and Epidemiology in Mental Health* 1, 3-9.

Eklund M., Hansson L. & Bejerholm U. (2001). Relationship between satisfaction with occupational factors and health-related variables in schizophrenia outpatients. *Social Psychiatry and Psychiatry Epidemiology* 36, 79-85.

Gaebel W (2004). Course, typologies, treatment principles, and research concepts. *Pharmacopsychiatry* 37, Suppl 2, 590-597.

Guy W. (1976). *ECDEU Assessment Manual for Psychopharmacology.* Revised. DHEW Publication No (ADM). US. National Institute of Health: Rockville.

Gaddini A., Franco F., Di Lallo D. & Biscaglia L. (2005). Hospitalisation for schizophrenia in acute psychiatric wards of the Lazio region: a 4-year follow-up study. *Epidemiologia e Psichiatria Sociale* 14(4), 227-234.

Harding C.M. & Keller A.B. (1998). Long term outcome of social functioning. In *Social Functioning in Schizophrenia* (ed. K. Mueser & N. Tarrier), pp 134-148. Allyn & Bacon: Needham Heights, MA.

Hodgins S., Tiihonen J. & Ross D. (2005). The consequences of conduct disorder for males who develop schizophrenia: association with criminality, aggressive behavior, substance use and psychiatric services. *Schizophrenia Research* 78, 323-335.

Junginger J. & McGuire L. (2004). Psychotic motivation and the paradox of current research on serious mental illness and rates of violence. *Schizophrenia Bulletin* 30, 21-30.

Kallert T.W., Leisse M. & Winiecki P. (2004). Needs for care of chronic schizophrenic patients in long term community treatment. *Social Psychiatric and Psychiatry Epidemiology* 39, 386-396.

Kay S.R., Abraham F. & Opler L.A. (1986). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* 13, 261-276.

Knapp M., Mangalore R. & Simon J. (2004). The global costs of schizophrenia. *Schizophrenia Bulletin* 30, 279-293.

Lehman A.F. (1998). Translating research into practice: the schizophrenia patients outcome research team (PORT) treatment recommendations. *Schizophrenia Bulletin* 24(1), 1-10.

Link B.G., Andrews H. & Cullen F. (1992). The violent and illegal behavior of mental patients reconsidered. *American Sociological Review* 52, 275-292.

Modestin J., Huber A., Satirli E., Malti T. & Hell D. (2003). Long-term course of schizophrenic illness: Bleuler's study reconsidered. *American Journal of Psychiatry* 160, 2202-2208.

Mueser K., Bond G. & Drake R. (1998). Models of community care for severe mental illness: a review of research on case management. *Schizophrenia Bulletin* 24, 37-74.

Norman R.M., Malla A.K., Cortese L., Cheng S., Diaz K., McIntosh E., McLean T.S., Rickwood A. & Voruganti L.P. (1999). Symptoms

and cognition as predictors of community functiong: a prospective analysis. *American Journal of Psychiatry* 156, 400-405.

Parker G. & Hadzi-Pavlovic D. (1995). The capacity of a measure of disability (the LSP) to predict hospital readmission in those with schizophrenia. *Psychological Medicine* 25, 157-163.

Raven J.C. (1984). *Matrici Colore Progressive* 1938. O.S.-Organizzazioni Speciali: Firenze.

Robins L.N. & Price R.K. (1991). Adult disorders predicted by childhood conduct problems: Results from the NIMH epidemiologic catchment area project. *Psychiatry* 54, 116-132.

Rosen A., Hadzi-Pavlovic D. & Parker G. (1989) The Life Skills Profile: a measure assessing function and disability in schizophrenia. *Schizophrenia Bulletin* 15, 325-337.

Ruggeri M., Lasalvia A., Bisoffi G., Thornicroft G., Vazquez-Barquero J.L., Becker T., Knapp M., Knudsen H.C., Schene A., Tansella M. & the Epsilon study group (2003). Satisfaction with mental health services among people with schizophrenia in five European sites: results from EPSILON study. *Schizophrenia Bulletin* 29, 229-245.

Ruggeri M., Lasalvia A., Tansella M., Bonetto C., Abate M., Thornicroft G., Allevi L. & Ognibene P. (2004). Heterogeneity of outcomes in schizophrenia 3-year follow-up of treated prevalent cases. *British Journal of Psychiatry* 18(4), 48-57.

Sytema S., Burgess P. & Tansella M. (2002). Does community care decrease length of stay and risk of rehospitalization in new patients with schizophrenic disorders? A comparative care register study in Groningen, the Netherlands; Victoria, Australia; and South Verona, Italy. *Schizophrenia Bulletin* 28, 273-281.

Taylor P.J., Leese M., Williams D., Butwell M., Daly R. & Larkin E. (1998). Mental disorder and violence: a special high security hospital study. *British Journal of Psychiatry* 172, 218-226.

Udechuku A., Olver J., Hallam K., Blyth F., Leslie M., Nasso M., Schlesinger P., Warren L., Turner M. & Burrows G (2005). Assertive community treatment of the mentally ill: service model and effectiveness. *Psychiatry Quarterly* 76(2), 97-106.

World Health Organization (1992). *Classification of Psychiatric and Behavioral Syndromes*, 10th Revision. WHO: Geneva.

Wykes T., Leese M., Taylor R. & Phelan M. (1998). Effects of community services on disability and symptoms. PRisM psychosis study 4. *British Journal of Psychiatry* 173, 385-390.

Zizolfi S., Santone G., Borsetti G. & de Girolamo G. (2004). La valutazione del funzionamento sociale negli ospiti delle SR. In *Le Strutture Residenziali e i loro Ospiti* (*Gruppo Nazionale PROGRES*). Il Pensiero Scientifico Editore: Roma.