Archives of Psychiatry and Psychotherapy, 2023; 2: 15–24

10.12740/APP/158201

Is depressed mood clinically relevant at the onset of schizophrenia? A longitudinal study

Lorenzo Pelizza, Emanuela Leuci, Emanuela Quattrone, Giuseppina Paulillo, Silvia Azzali, Simona Pupo, Pietro Pellegrini

Abstract

Aim: Depressed mood (DM) in schizophrenia is often associated with suicide risk and poor outcomes. However, it is generally overlooked in clinical practice, especially in First Episode Schizophrenia (FES). The aims of this investigation were: (1) to calculate baseline prevalence of FES patients with relevant DM, (2) to longitudinally monitor DM severity levels over a 12-month follow-up, and (3) to investigate their associations with clinical data and the specific treatment components of an "Early Intervention in Psychosis" (EIP) program.

Material and Methods: The Positive and Negative Syndrome Scale (PANSS) was completed by all FES participant. Individuals with a baseline PANSS "Depression" item subscore of ≥ 5 were classified as having relevant depressed mood (FES/DM+). Chi-square and Mann-Whitney tests were used for inter-group comparisons. A linear regression analysis was also performed.

Results: Fifty-three (33.3%) participants were in the FES/DM+ subgroup. Relevant DM at baseline was associated with female gender and a higher PANSS "Positive Symptoms" score. Across the follow-up, FES individuals improved their DM severity levels. This was significantly related to a longitudinal decrease in PANSS "Positive Symptoms" levels.

Conclusions: DM is relatively frequent in FES, already at the recruitment in EIP services. However, its severity decreases overtime within specialized EIP programs.

depression; first episode schizophrenia; follow-up; early intervention; treatment response

INTRODUCTION

Depressive psychopathology is a frequent comorbid condition in First Episode Schizophrenia (FES) [1]. In particular, clinically relevant *Depressed Mood* (DM) in FES seems to be significantly related to poor real-world performance [2] and is one of the stronger predictors for suicidal thinking and behavior, even more than command hallucinations [3]. However, DM is still often *overlooked* in the clinical practice with young people with FES, also due to the greater importance attributed to positive and negative

Lorenzo Pelizza[1,2], Emanuela Leuci[1], Emanuela Quattrone[1], Giuseppina Paulillo[1], Silvia Azzali[3], Simona Pupo[4], Pietro Pellegrini[1]: [1]Department of Mental Health and Pathological Addiction, Azienda USL di Parma, Parma, Italy; [2]Department of Biomedical and NeuroMotor Sciences, "Alma Mater Studiorum" Università degli Studi di Bologna, Bologna, Italy; [3]Department of Mental Health and Pathological Addiction, Azienda USL-IRCCS di Reggio Emilia, Italy; [4]Division of Pain Medicine, Department of Medicine and Surgery, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy.
Correspondence address: lorenzo.pelizza@unibo.it

symptoms, and to the uncertainty on its clinical significance and etiopathogenesis [4]. Moreover, empirical studies investigating the treatment of DM in FES was relatively poor [5, 6]. In particular, very few evidence was found on DM response to treatment and its influence on discharge outcomes in people at the onset of schizophrenia (i.e., FES) enrolled within "Early Intervention in Psychosis" (EIP) programs [7].

Thus, the *aims* of this investigation were threefold:

1) to calculate the baseline prevalence rate of FES subjects with relevant DM and to compare their clinical and socio-demographic data with FES individuals without relevant levels of DM;
2) to monitor the longitudinal stability of DM in the FES total sample over a 1-year follow-up period within a specialized (real world) EIP protocol;
3) to examine any significant association of DM with sociodemographic data, clinical features and the specialized EIP treatment components both at baseline and over the 12 months of follow-up.

No longitudinal studies specifically focused on relevant DM and its response to EIP treatments in Italian FES subjects has been reported in the literature to date.

MATERIAL AND METHODS

Setting and Subjects

Subjects were recruited between January 2013 and June 2019 within the "Parma-Early Psychosis" (*Pr-EP*) protocol, i.e., an evidence-based, recovery-oriented EIP program specifically implemented in all community adolescent and adult mental health services of the Parma Department of Mental Health, in Italy [8-9].

Inclusion criteria were: (1) specialist help-seeking request; (2) age between 12 and 35 years; (3) presence of FES in accordance with the DSM-IV-TR diagnostic criteria [10]; and (4) a DUP (i.e. "Duration of Untreated Psychosis" defined as the time interval [in weeks] between the onset of full-blown psychotic symptoms and the first antipsychotic intake) [11] of < 2 years. This DUP length was chosen because it is usually considered as the time limit to helpfully provide specialized interventions within the EIP paradigm [12].

Exclusion criteria were: (1) past psychotic episode within a DSM-IV-TR diagnosis of both affective and non-affective psychosis; (2) past exposure to antipsychotic drug or first antipsychotic intake for more than 2 months in the current psychotic episode; (3) current substance dependence in accordance with the DSM-IV-TR diagnostic criteria; (4) neurological disorder or any other medical illness manifesting with psychiatric features; and (5) known intellectual disability (i.e. intelligence quotient < 70). In the present investigation, we decided to consider past exposure to antipsychotic drugs in a past illness episode (and thus before the Pr-EP recruitment) as a functional equivalent of a past psychotic episode in line with what was suggested by Yung and colleagues [13], who defined the psychosis threshold within the EIP paradigm as essentially that at which antipsychotic drugs would probably be started in the common clinical practice [14].

All individuals (and their parents, if minors) gave their written informed consent prior to their recruitment in this research. Relevant ethical approvals were obtained for this investigation (AVEN protocol n. 36102/09.09.2019). This research was also carried out in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments.

Assessment and measures

In the present investigation, the psychopathological evaluation included the Positive and Negative Syndrome Scale (PANSS) [15] and the Global Assessment of Functioning (GAF) scale [10]. These instruments were completed by trained Pr-EP team members both at baseline and after the 12 months of follow-up. Supervisions and score workshops ensured the inter-rater reliability of such tools. Finally, a sociodemographic and clinical schedule (including information on gender, age at baseline, education, ethnic group, past hospitalization, current substance abuse, DUP, past specialist contact and the provision intensity of the Pr-EP treatment components) was also filled in at entry [16].

The *PANSS* is a widely used clinical interview to assess the severity of schizophrenia psychopa-

thology. It showed good psychometric properties also in young Italian people with early psychosis [17-19]. In the current investigation, we considered a PANSS "Depression" G6 item subscore of ≥ 5 (i.e., at least "a distinctly depressed mood that is associated with obvious sadness, pessimism, loss of social interest, psychomotor retardation and interference in appetite and sleep") [15] as an index of relevant DM. Furthermore, as suggested by Shafer and Dazzi [20] in their recent meta-analysis on the PANSS factor configuration, we also considered the following four main psychopathological dimensions of schizophrenia psychopathology: "Positive Symptoms", "Negative Symptoms", "Disorganization" and "Resistance/Activation".

The *GAF* is one of the most common scales for evaluating clinical and socio-occupational functioning in FES patients. It showed good psychometric properties also in young Italian people with early psychosis [21, 22].

Procedures

The axis-I diagnosis was formulated by trained Pr-EP team members using the Structured Clinical Interview for DSM-IV-TR axis I Disorders (SCID-I) [23]. The Pr-EP program indicates that FES individuals should be assigned to a multi-professional team (including a psychiatrist, a case-manager for early recovery-oriented rehabilitation and a clinical psychologist) usually within three weeks after their baseline assessment [24]. Specifically, in accordance with their clinical severity, FES patients should be provided with a 2-year comprehensive intervention program including psychopharmacological therapy and a multi-component psychosocial treatment (combining intensive case management focused on early recovery, psychoeducational meetings for family members and an individual psychotherapy based on cognitive-behavioral models), as suggested by the current guidelines on the topic [25]. Antidepressants and benzodiazepines could also be prescribed to treat insomnia, anxiety and/or depressive symptoms.

Low-dose atypical *antipsychotic* drug was administered as first-line therapy [26]. In accordance with the "Defined Daily Doses" method proposed by Leucht and co-wokers [27], the daily dose of different antipsychotics was standardized and reported as equivalent dose of chlorpromazine (mg/die). For *antidepressants*, we referred to a relatively recent meta-analysis on dose equivalence of antidepressant medications reported as equivalent dose of fluoxetine (mg/day), which was based on a method assuming the optimum doses found in double-blind, flexible-dose trials to be equivalent [28].

Psychoeducational sessions for family members were inspired by the model proposed by Kuipers and colleagues [29], combining psychological support and problem-solving modules. Eight cognitive-behavioral-oriented meetings with each family should be offered in the first 6 months of treatment [30].

Case management aimed at promoting early recovery and at preventing long-term disability [31]. Two sessions per month (each lasting 60 minutes) should be provided in the first year of treatment [32].

Individual psychotherapy was based on the modules proposed by Fowler and co-workers [33], including psychoeducation on depressive features, anxiety and psychological distress. Ten sessions (each lasting 60 minutes) should be provided in the first year of treatment [34].

Finally, participants having a baseline PANSS "Depression" item subscore of ≥ 5 were classified as FES individuals with relevant depressed mood (FES/DM+). The remaining FES subjects were considered as not having a relevant DM at entry and were grouped in the FES/DM – subsample.

Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS) for Windows, version 15.0 [35]. All tests were two-tailed, with significance level set at 0.05. In between-group comparisons, the Mann-Whitney U test was used to investigate continuous parameters, while the Chi-square test was used to assess categorical variables. The Wilcoxon test for repeated measures was performed on the FES total sample to examine the 1-year longitudinal stability of DM severity levels. A binary logistic regression analysis with the dichotomized PANSS "Depression" item score (cut-off ≥ 5) as the dependent

parameter and clinical features and sociodemographic data as independent variables was carried out in the FES total population. Moreover, a linear regression analysis with PANSS "Depression" item score as the dependent measure and Pr-EP treatment components, clinical and sociodemographic data as independent parameters was also performed in the FES total group along the 1-year follow-up period. Specifically, in our longitudinal analyses, we decided to consider the differences (deltas [Δ]) between PANSS scores at entry (T0) and at the 1-year assessment time point (T1) as primary clinical variables to investigate overtime. Indeed, in line with what was proposed by Ver Hoef [36], the delta scores better describe the temporal dynamics and longitudinal changes of schizophrenia psychopathology in comparison with T0 and T1 single measures.

RESULTS

Over the course of this investigation, 159 FES participants were enrolled. Their clinical, sociodemographic and pharmacological data are shown in the Table 1. Fifty-three (33.3%) FES individuals had a baseline PANSS "Depression" item subscore of ≥ 5 and were group in the FES/DM+ subsample. At entry, antidepressant prescription rate in the FES total group was 6.9% (n = 11).

Table 1. Sociodemographic data and clinical features of the FES total group and the two subsamples.

Variable	FES total group (n = 159)	FES/DM+ (n = 53)	FES/DM- (n = 106)	X^2/z
Gender (female)	43 (27.0%)	20 (37.7%)	23 (21.7%)	4.606***
Ethnic group (white Caucasian)	130 (81.8%)	43 (81.1%)	87 (82.1%)	0.021
Age at entry (in years)	23.29 ± 5.36	22.87 ± 5.44	23.50 ± 5.33	-0.743
Education (in years)	11.54 ± 2.69	11.47 ± 2.49	11.58 ± 2.79	-0.325
DUP (in weeks)	49.46 ± 48.48	52.25 ± 54.16	48.07 ± 45.58	-0.375
Hospitalization (as source of Pr-EP referral)	86 (54.1%)	29 (54.7%)	57 (53.8%)	0.013
Past specialist contact	80 (50.3%)	22 (41.5%)	48 (45.3%)	2.466
Substance misuse (at entry)	72 (45.3%)	23 (43.4%)	49 (46.2%)	0.114
T0 PANSS "Positive Symptoms" factor score	18.54 ± 6.00	20.57 ± 6.02	17.53 ± 5.76	-3.372*
T0 PANSS "Negative Symptoms" factor score	26.13 ± 8.54	28.06 ± 8.11	25.17 ± 8.63	-1.854
T0 PANSS "Disorganization" factor score	19.86 ± 7.44	19.58 ± 7.73	19.99 ± 7.32	-0.338
T0 PANSS "Activation/Resistance" factor score	9.63 ± 4.78	9.06 ± 5.34	9.92 ± 4.48	-1.810
T0 GAF score	42.52 ± 10.14	39.08 ± 10.63	44.24 ± 9.47	-2.990**
T0 equivalent dose of chlorpromazine (mg/day)	232.20 ± 174.00	241.80 ± 225.00	227.40 ± 141.80	-0.514
T0 equivalent dose of fluoxetine (mg/day)	45.00 ± 22.52	51.43 ± 25.45	35.00 ± 12.91	-2.259*
T0 antipsychotic prescription rate	145 (91.2%)	45 (84.9%)	100 (94.3%)	3.916
T0 antidepressant prescription rate	11 (6.9%)	7 (13.2%)	4 (3.8%)	4.883***
T1	(n = 135)	(n = 36)	(n = 99)	0.245
T1 Hospitalization rate	37 (27.4%)	11 (30.6%)	26 (26.3%)	0.483
T1 antipsychotic prescription rate	124 (97.9%)	32 (88.9%)	92 (92.9%)	0.249
T1 antidepressant prescription rate	9 (6.7%)	4 (11%)	5 (5.1%)	

Note. FES = First Episode Schizophrenia; FES/DM+ = FES patients with relevant clinical depression; FES/DM – = FES patients without relevant clinical depression; DUP = Duration of Untreated Psychosis; Pr-EP = "Parma-Early Psychosis" program; PANSS = Positive And Negative Syndrome Scale; GAF = Global Assessment of Functioning; T0 = baseline assessment; T1 = 1-year assessment time point. Frequencies (percentages), mean ± standard deviation, Chi-squared test (X2) and Mann-Whitney test (z) values are reported. *p < 0.001; **p < 0.01; ***p < 0.05. Statistically significant results are in bold.

Baseline data

Compared to FES/DM-, FES/DM+ patients showed at entry a greater percentage of females, a higher PANSS "Positive Symptoms" score and a lower GAF score (Table 1). Moreover, they had a greater baseline antidepressant prescription rate and a higher baseline equivalent dose of fluoxetine.

Furthermore, our binary logistic regression analysis results showed that the baseline presence of a PANSS "Depression" item cut-off score of ≥ 5 (i.e. the presence of relevant DM at entry) was significantly predicted by higher baseline levels of PANSS "Positive Symptoms" dimension score (Table 2). The overall percentage of dichotomized ascription using this model for predicting relevant baseline DM in FES participants was 73.6%.

Table 2. Binary logistic regression results of the dichotomized PANSS "Depression" item score (cut-off ≥ 5) by sociodemographic data and clinical features within the FES total sample (n = 159) at baseline.

Variable	B	SE	Wald	df	p	OR	95% CI for OR(B) Lower	Upper
Gender (male)	-0.613	0.472	1.685	1	0.194	0.542	0.215	1.367
Age at entry (in years)	-0.019	0.039	0.249	1	0.618	0.981	0.909	1.059
Education (in years)	-0.075	0.082	0.858	1	0.354	0.927	0.790	1.088
Ethnic group (white Caucasian)	-0.021	0.494	0.002	1	0.966	0.979	0.372	2.577
Previous Hospitalization	-0.317	0.406	0.612	1	0.434	0.728	0.329	1.612
Past specialist contact	-0.406	0.404	1.009	1	0.315	0.666	0.302	1.472
DUP (in weeks)	0.005	0.004	1.449	1	0.229	1.005	0.997	1.013
Substance misuse (at entry)	0.126	0.455	0.076	1	0.783	1.134	0.464	2.768
PANSS "Positive Symptoms" factor score	0.127	0.038	10.998	1	0.001	1.136	1.053	1.224
PANSS "Negative Symptoms" factor score	0.057	0.029	3.832	1	0.059	1.059	1.000	1.122
PANSS "Disorganization" factor score	-0.069	0.035	3.835	1	0.059	0.933	0.871	1.000
PANSS "Activation/Resistance" factor score	-0.087	0.045	3.755	1	0.063	0.916	0.839	1.001
GAF score	-0.039	0.020	3.754	1	0.063	0.961	0.924	1.000
Constant	1.028	1.810	0.323	1	0.570	2.797	-	-
Overall model fit test → X^2 = 33.339; p = 0.002								
Associated strength → Cox–Snell R^2 = 0.189, Negelkelke R^2 = 0.263								

Note. FES = First Episode Schizophrenia; DUP = Duration of Untreated Psychosis; PANSS = Positive And Negative Syndrome Scale; GAF = Global Assessment of Functioning; B = regression coefficient; SE = standard error; Wald = Wald statistic value; df = degrees of freedom; OR = odd ratio; 95% CI = 95% confidence intervals for odd ratio; X2 = Chi-square value; R2 = R-squared or coefficient of determination; p = statistical significance; p-value lower than 0.05 are reported as bold values.

Follow-up data

Over the course of this investigation, 24 (15.1%) FES participants did not reach the T1 assessment for the re-administration of the Pr-EP evaluation battery. Specifically, eleven (6.9% of the FES group at baseline) dropped out the Pr-EP protocol and 13 moved out from the catchment area and it was not possible to reach them for completing the final assessment battery. At T1, the median of case management meetings was 10 (interquartile range [IR] = 5-21), the median of individual psychotherapy sessions was 10 (IR = 5-17) and the median of family psychoeducation sessions was 5 (IR = 1-10). The T1 pharmacological data are shown in the Table 1. In particular, antidepressants were still prescribed to 9 (6.7%) FES participants who ended the follow-up.

Along the 1-year follow-up period, a significant reduction in the PANSS "Depression" item subscore was observed (Table 3). Our linear regression analysis results showed that the delta

decrease between T0 and T1 PANSS "Depression" item subscores was significantly predicted by the delta reduction between T0 and T1 PANSS "Positive Symptoms" dimension scores (Table 4).

Table 3 – Longitudinal course of the PANSS "Depression" item subscores across the 1-year follow-up period in the FES total sample (n = 135).

Variable	Baseline	1-year follow-up assessment time	z
PANSS "Depression" item scores	3.54 ± 1.58	2.46 ± 1.32	-7.125[a]

Note. PANSS = Positive And Negative Syndrome Scale; FES = First Episode Schizophrenia; mean ± standard deviation, Wilcoxon test (z) values are reported; *p value < 0.001. Statistically significant results are in bold.

Table 4. Linear regression analysis results of the difference (delta) in T0 and T1 PANSS "Depression" item subscores by clinical features and specialized treatment components of the Pr-EP program across the 1-year follow-up period in the FES total sample.

T0-T1 Delta PANSS "Depression" G6 item subscores (n = 135)	B	SE	95% CI for B Lower	Upper	β	p	R^2 = 0.310 $F_{[df=12]}$ = 4.535 p = 0.0001
Constant	0.517	0.295	-0.067	1.101	-	0.082	
T0 equivalent dose of Chlorpromazine (mg/day)	0.052	0.051	-0.049	0.152	0.097	0.309	
T1 equivalent dose of Chlorpromazine (mg/day)	-0.001	0.015	-0.030	0.028	-0.006	0.944	
T0 equivalent dose of Fluoxetine (mg/day)	-0.073	0.049	-0.170	0.024	-0.147	0.140	
T1 equivalent dose of Fluoxetine (mg/day)	0.012	0.009	-0.006	0.029	0.103	0.198	
T1 number of individual psychotherapy sessions	-0.020	0.018	-0.056	0.016	-0.109	0.281	
T1 number of psychoeducational sessions for family members	-0.005	0.024	-0.052	0.042	-0.018	0.847	
T1 number of case management sessions	0.003	0.006	-0.009	0.015	0.040	0.624	
T0-T1 Delta PANSS "Positive Symptoms" scores	0.068	0.029	0.010	0.126	0.284	0.023	
T0-T1 Delta PANSS "Negative Symptoms" scores	0.042	0.022	-0.001	0.085	0.211	0.058	
T0-T1 Delta PANSS "Disorganization" scores	0.006	0.030	-0.053	0.065	0.023	0.841	
T0-T1 Delta PANSS "Activation/Resistance" scores	-0.014	0.039	-0.092	0.064	-0.034	0.722	
T0-T1 Delta GAF scores	-0.014	0.014	-0.042	0.014	-0.113	0.330	

Note. T0 = Baseline; T1 = 1-year assessment time; T2 = 2-year assessment time; PANSS = Positive And Negative Syndrome Scale; Pr-EP = Parma-Early Psychosis Program; FES = First Episode Schizophrenia; GAF = Global Assessment of Functioning; B = regression coefficient, SE = standard error, 95% CI= 95% Confident Intervals for B, β = standardized regression coefficient; p = statistical significance, R2 = R-squared or coefficient of determination, F = statistic test value for linear regression, df = degrees of freedom. Statistically significant p values are in bold.

DISCUSSION

The results of this research show that more than 1/3 of FES subjects had *relevant DM* already at the recruitment in an EIP service. In this respect, previous studies on young FES people reported a 38% prevalence of individuals having clinically significant levels of depressive psychopathology at baseline [37] and a 26% pooled prevalence of depressive disorder at entry in accordance with gold-standard diagnostic criteria [1]. These findings overall suggest that DM in FES is often serious enough to justify an in-depth psychopathological evaluation and a timely clinical intervention [38].

However, an *antidepressant prescription* rate of only 13.2% was observed in the FES/DM+ subgroup at entry, and an approximately 7% rate was found in the FES total population. These results are substantially in line with what was found in a longitudinal investigation on concomitants of depression in FES, reporting a 5% prescription rate of antidepressant drugs [39]. Overall, this evidence suggests that relevant

DM in FES subjects is usually *undertreated*, also probably due to the emphasis on treating positive and negative symptoms, and to the traditionally held belief that schizophrenia is a "non-affective" disorder [40].

In the current investigation, DM was significantly associated with the following sociodemographic and clinical characteristics:

(a) *Greater percentage of females*: this result is not completely in line with findings reported in the current literature, which overall observed higher prevalence of caseness for depressive symptoms in FES males [41, 42]. Given that women usually show higher levels of internalizing symptoms (and lower levels of externalizing/substance abuse behaviors) in case of coping with traumatic experiences and psychopathological features [43], DM in FES females could also be due to the negative cognitive appraisals of the experience and the meaning of schizophrenia early onset. Indeed, the unfavorable impact and the disruption that FES potentially has on their vocational/educational goals, their identity construction and their interpersonal relationships could be particularly crucial during the critical developmental phase of adolescence and young adulthood [44].

(b) Higher levels of *positive symptoms*: in this investigation, the positive dimension was a statistically relevant psychopathological predictor of the presence of DM in FES subjects already at the recruitment time in our EIP protocol. In this respect, Phahladira and colleagues [39] suggested that the association between depressive and positive symptoms in FES is important at a "symptom-level". In this sense, clinically relevant depression could reflect state-related fluctuations in positive symptoms of FES, so as to follow the longitudinal course of positive dimension overtime [1]. However, DM in FES could also be due to the intrinsic illness progress of schizophrenia [45] and considered not only as a superimposed comorbidity, but also as an intrinsecable symptom dimension of the schizophrenic disorder. In our study, this was partly supported by the statistically relevant association between PANSS "Depression" and "Guilty feelings" item scores (B regression coefficient = 1.132, Odd Ratio = 3.103, p = 0.0001), in addition to the significant relationship between PANSS "Depression" and "Hallucinations" item subscores (B = 0.437, Odd Ratio = 1.549, p = 0.016) (for details, see also supplementary materials [Table S1]). Indeed, guilty feelings are of great importance in the primary psychopathological construct of clinical depression.

(c) Higher *functioning decline*: previous studies on this topic were mixed, with some findings showing functioning impairment in FES subjects with clinically relevant DM [46], and others reporting no association [4]. These conflicting results could be associated with third variables that may mediate this relationship (e.g. personality traits, neurocognitive development) [47].

Furthermore, the findings of this investigation showed a statistically significant *decrease in DM severity levels* across the 12-month follow-up period. This is in line with what was recently reported by Phahladira and co-workers [39], who found that depressive symptoms in FES individuals were highest at baseline, with the most significant reduction during the first 3 months of intervention and improvement maintenance along 2 years of follow-up. In the current research, this decrease was positively associated with the longitudinal severity reduction in positive symptom levels. This further supports what was recently suggested by Herniman and colleagues [1], who hypothesized that DM in FES strictly follows the longitudinal course of positive dimension overtime, reflecting their state-related fluctuations.

Finally, it should be emphasized the lack of association between DM severity levels and *negative symptoms* in our FES sample. This result is not concordant with what was reported by Chiappelli and co-workers [47], suggesting a basic link relationship between depressive and negative features in FES, partly attributable to their phenomenological overlap and/or to the presence of secondary negative symptoms as consequences of clinical depressed mood.

Limitations

A major limitation of this study was related to the relatively small sample size (especially for

the FES/DM+ subgroup). Therefore, further research on largest population of young FES patients with relevant baseline DM is needed.

Moreover, we examined FES subjects in a real-world care setting primarily focused at providing EIP interventions within standard community mental health services. Therefore, our findings can be compared exclusively to similar populations. In addition, even if a strength of this research could be the recruitment of FES participants at the illness onset, our results cannot be generalized to individuals at different phase of the disorder (e.g. people with prolonged schizophrenia).

Third, the current study was conducted within an EIP protocol not specifically focused on depression and depressed mood in FES. Indeed, schizophrenia psychopathology was evaluated with the PANSS, a scale widely used in FES samples, but poorly articulated for measuring depressive features. Moreover, DM was assessed with a single item score. This measure certainly underestimates the complexity of depression psychopathological facets, focusing only on DM (a major but non-exhaustive component of clinical depression). So, future investigations examining depression with more specific and reliable tools (such as the Calgary Depression Scale for Schizophrenia [CDSS]) [48] are needed. However, given the widespread use of the PANSS in FES research, our study has the potential to be replicated in similar populations, and this is of primary clinical importance, since investigations exploring beneficial effects of EIP treatments on depression and DM at the schizophrenia onset are still relatively poor, and higher levels of baseline DM are related to suicide risk and negative outcomes [49-51].

Finally, our treatment measures were not randomly assigned. This restricts our ability to draw causal conclusion on the observed associations both at baseline and as longitudinal changes in DM severity levels. Indeed, these relationships could also be due to other plausible explanations (e.g., FES patients with more serious psychopathology could receive more intensive treatments and improve the most, in part because they had the most to improve).

Conclusions

Clinically relevant DM is relatively common in FES, affecting approximately 1/3 of patients. However, it is often overlooked in the common clinical practice. Thus, an in-depth, comprehensive assessment of comorbid DM (and depressive symptoms in general) is crucial already at the recruitment time of FES individuals in specialized EIP services, as well as a timely clinical intervention, specifically in order to reduce suicide risk and to improve long-term outcomes. The results of this research also showed a longitudinal improvement in DM of FES patients together with the overtime reduction in positive symptoms (but not with antipsychotic and antidepressant dosage both at presentation and at the end of our follow-up period). On the contrary, antidepressants were under-prescribed (and DM was thus under-treated) in our FES subgroup with clinically relevant DM (interesting approximately 10% of FES/DM+ participants). Therefore, specialized targeted interventions (both pharmacological and psychosocial) on DM in people with FES are recommended.

Acknowledgments

This research received no specific grant from any funding agencies in the public, commercial or not-for-profit sectors. The "Parma Early Psychosis" (Pr-EP) program was partly financed through a special, treatment-oriented regional fund: "Progetto Esordi Psicotici della Regione Emilia Romagna".

For their facilitating technical and administrative support in the Pr-EP program, the authors gratefully acknowledge the "Early Psychosis Facilitators Group" members of the Parma Department of Mental Health and Pathological Addictions. The authors also wish to thank all the patients and family members who actively participated to the Pr--EP program.

Declaration of interest

The authors report no conflict of interest.

REFERENCES

1. Herniman S, Allott K, Phillips L, Wood S, Uren J, Mallawaarachchi S, Cotton S. Depressive psychopathology in first-episode schizophrenia spectrum disorders: a systematic review, meta-analysis and meta-regression. Psychol Med. 2019; 49: 2463-2474.
2. Chen XJ, Wang DM, Zhou HX, Zhu RR, Tian Y, Du YX, Chen JJ, Chen DC, Wang L, Zhang XJ. Association of depressive symptoms with cognitive impairment in patients with never-treated first-episode schizophrenia: analysis of the Depression in Schizophrenia in China (DISC) study. Gen Hosp Psychiatry. 2021; 71:108-113.

3. Pelizza L, Pellegrini C, Quattrone E, Azzali S, Landi G, Pellegrini P, Leuci E. Suicidal thinking and behavior in first episode schizophrenia: findings from the 24-month follow-up of the "Parma Early Psychosis" program. Arch Suicide Res. 2020; 24: 1-21.
4. Cotton SM, Lambert M, Schimmelmann BG, Mackinnon A, Gleeson JFM, Berk M, Hides L, Chanen A, McGorry PD, Conus P. Depressive symptoms in first episode schizophrenia spectrum disorder. Schizophr Res. 2012; 134: 20-26.
5. Coentre R, Talina MC, Gois C, Figueira ML. Depressive symptoms and suicidal behavior after first-episode psychosis: a comprehensive systematic review. Psychiatry Res. 2017; 253: 240-248.
6. Pelizza L, Maestri D, Leuci E, Quattrone E, Azzali S, Paulillo G, Pellegrini P. Individual psychotherapy can reduce suicidal ideation in first episode psychosis: further findings from the 2-year follow-up of the "Parma Early Psychosis" programme. Clin Psychol Psychother. 2021; https://doi.org/10.1002/cpp.2678.
7. Upthegrove R, Marwaha S, Birchwood M. Depression and schizophrenia: cause, consequence, or trans-diagnostic issue? Schizophr Bull. 2017; 43: 240-244.
8. Leuci E, Quattrone E, Pellegrini P, Pelizza L. The "Parma-Early Psychosis" program: general description and process analysis. Early Interv Psychiatry. 2020; 14: 356-364.
9. Landi G, Leuci E, Quattrone E, Azzali S, Pellegrini C, Pellegrini P, Pelizza L. The "Parma-Early Psychosis" programme: characterization of help-seekers with first episode psychosis. Early Interv Psychiatry. 2021; 15: 380-390.
10. American Psychiatric Association (APA). Diagnostic and Statistical Manual of mental disorders, IV edition, Text Revision (DSM-IV-TR). Washington DC: APA Press; 2000.
11. Woods SW, Yung AR, McGorry PD, McGlashan TH. Duration of untreated psychosis: getting both the timing and the sample right. Am J Psychiatry. 2020; 177: 1183.
12. Poletti M, Pelizza L, Azzali S, Paterlini F, Garlassi S, Scazza I, Chiri LR, Pupo S, Raballo A. Overcoming the gap between child and adult mental health services: the Reggio Emilia experience in an early intervention in psychosis program. Early Interv Psychiatry. 2021; 15: 1749-1758.
13. Yung AR, Yuen YP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, Francey SM, Cosgrave EM, Killackey E, Stanford C, Godfrey K, Buckby J. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. Aust N Z J Psychiatry. 2005; 39: 964-971.
14. Paterlini F, Pelizza L, Galli G, Azzali S, Scazza I, Garlassi S, Chiri LR, Poletti M, Pupo S, Raballo S. Interrater reliability of the authorized Italian version of the Comprehensive Assessment of At-Risk Mental States (CAARMS-ITA). J Psychopathol. 2019; 25: 24-28.
15. Kay SR, Fiszbein A, Opler LA. The Positive And Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophr Bull. 1987; 13: 261-276.
16. Pelizza L, Pellegrini C, Quattrone E, Azzali S, Landi G, Pellegrini P, Leuci E. Suicidal ideation in patients experiencing a first-episode psychosis: findings from the 2-year follow-up of the "Parma Early Psychosis" program. Suicide Life Threat Behav. 2020; 50: 838-855.
17. Tonna M, Ossola P, Marchesi C, Bettini E, Lasalvia A, Bonetto C, Lenzi J, Rucci P, Iozzino L, Cellini M, Comacchio C, Cristofalo D, D'Agostino A, de Girolamo G, De Santi K, Ghigi D, Leuci E, Miceli M, Meneghelli A, Pileggi F, Scarone S, Santonastaso P, Torresani S, Tosato S, Veronese A, Fioritti A, Ruggeri M, GET UP Group. Dimensional structure of first episode psychosis. Early Interv Psychiatry. 2019; 13: 1431-1438.
18. Pelizza L, Azzali S, Paterlini F, Garlassi S, Scazza I, Chiri LR, Poletti M, Pupo S, Raballo A. Negative symptom dimensions in first episode psychosis: is there a difference between schizophrenia and non-schizophrenia spectrum disorders? Early Interv Psychiatry. 2021; 15: 1513-1521.
19. Leuci E, Pelizza L, Landi G, Quattrone E, Maestri D, Azzali S, Pelosi A, Ceroni P, Soncini C, Daolio MC, Paulillo G, Raballo A, Pellegrini P. Personal health budget in patients with first episode psychosis: a new rehabilitation model based on a community care system in Italy. Early Interv Psychiatry. 2022; 16: 221-230.
20. Shafer A, Dazzi F. Meta-analysis of the Positive and Negative Syndrome Scale (PANSS) factor structure. J Psychiatr Res. 2019; 115: 113-120.
21. Poletti M, Pelizza L, Azzali S, Paterlini F, Garlassi S, Scazza I, Chiri LR, Gebhardt E, Pupo S, Raballo A. Clinical high risk for psychosis in childhood and adolescence: findings from the 2-year follow-up of the ReARMS project. Eur Child Adolesc Psychiatry. 2019; 28: 957-971.
22. Pelizza L, Leuci E, Landi G, Maestri D, Paulillo G, Ceroni P, Soncini C, Daolio MC, Quattrone E, Pellegrini P. Personal health budget as a new rehabilitation model for severe mental illness within a caring community: an Italian evaluation study of beneficial effects. Aust N Z J Psychiatry. 2021; 55: 602-612.
23. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR axis I Disorders (SCID-I). New York (NY): New York State Psychiatric Institute; 2002.
24. Pelizza L, Leuci E, Maestri D, Quattrone E, Azzali S, Paulillo G, Pellegrini P, Raballo A. Disorganization in first episode schizophrenia: treatment response and psychopathological findings from the 2-year follow-up of the "Parma Early Psychosis" program. J Psychiatr Res. 2021; 141: 293-300.
25. National Institute for health and Care Excellence (NICE). Psychosis and schizophrenia in children and young people: recognition and management. Leicester: NICE Press; 2016.
26. Barnes TR, Drake R, Paton C, Cooper SJ, Deakin B, Ferrier IN, Gregory CJ, Haddad PM, Howes OD, Jones I, Joyce EM, Lewis S, Lingford-Hughes A, MacCabe JH, Owens DC, Patel MX, Sinclair JM, Stone JM, Talbot PS, Upthegrove R,

Wieck A, Yung AR. Evidence-based guidelines for the pharmacological treatment of schizophrenia: updated recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2020; 34: 3-78.

27. Leucht S, Samara M, Heres S, Davis JM. Dose equivalents for antipsychotic drugs: the DDD method. Schizophr Bull. 2016; 42 (suppl. 1): S90-S94.
28. Furukawa TA, Cipriani A, Cowen PJ, Leucht S, Egger M, Salanti G. Optimal dose of selective serotonin re-uptake inhibitors, venlafaxine, and mirtazapine in major depression: a systematic review and dose-response meta-analysis. Lancet Psychiatry. 2019; 6: 601-609.
29. Kuipers E, Leff J, Lam D. Family work for schizophrenia: a practical guide. London: Gaskell; 2002.
30. Pelizza L, Leuci E, Maestri D, Quattrone E, Azzali S, Paulillo G, Pellegrini P. Examining disorganization in patients with first episode psychosis: findings from a 1-year follow-up of the "Parma Early Psychosis" program. Early Interv Psychiatry. 2021; 16: 552-560.
31. Wong HH, Yong YH, Shahwan S, Cetty L, Vaingankar J, Hon C, Lee H, Loh C, Abdin E, Subramaniam M. Case management in early psychosis intervention programme: perspectives of clients and caregivers. Early Interv Psychiatry. 2019; 13: 598-603.
32. Pelizza L, Maestri D, Leuci E, Quattrone E, Azzali S, Paulillo G, Pellegrini P. Negative symptom configuration within and outside schizophrenia spectrum disorders: results from the "Parma Early Psychosis" program. Psychiatry Res. 2020C; 294: 113519. https://doi.org/10.1016/j.psychres.2020.113519.
33. Fowler D, Garety P, Kuipers E. Cognitive behavior therapy for psychosis. London: Wiley; 1995.
34. Pelizza L, Leuci E, Maestri D, Quattrone E, Azzali S, Paulillo G, Pellegrini P. Longitudinal persistence of negative symptoms in young individuals with first episode schizophrenia: a 24-month multi-modal program follow-up. Nord J Psychiatry. 2021; https://doi.org/10,1080/08039488.2021.2015431.
35. SPSS Inc. Statistical Package for Social Science (SPSS) for Windows, version 15.0. Chicago (IL): SPSS Inc. Press; 2010.
36. Ver Hoef JM. Who invented the delta method? Am Stat. 2012; 66: 124-127.
37. Rybakowski JK, Vansteelandt K, Szafranki T, Thys E, Jarema M, Fleischhacker WW, Kahn RS, Peuskens J, EUFEST Study Group. Treatment of depression in first episode of schizophrenia: results from EUFEST. Eur Neuropsychopharmacol. 2021; 22: 875-882.
38. Pelizza L, Pompili M, Azzali S, Paterlini F, Garlassi S, Scazza I, Chiri LR, Poletti M, Pupo S, Raballo A. Suicidal thinking and behavior in first episode psychosis: findings from a 3-year longitudinal study. Early Interv Psychiatry. 2021; 15: 624-633.
39. Phahladira L, Asmal L, Luckhoff HK, du Plessis, S, Scheffler F, Kilian S, Smit R, Buckle C, Chiliza B, Emsley R. The course and concomitants of depression in first-episode schizophrenia spectrum disorders: a 24-month longitudinal study. Psychiatry Res. 2021; 298: 113767. https://doi.org/10.1016/j.psychres.2021.113767.
40. Raballo A, Poletti M. Towards a phenomenological and developmental clinical staging of the mind with psychosis. Lancet Psychiatry. 2121; 8: 277-278.
41. Romm KL, Rossberg JL, Berg AO, Barnett EA, Faerden A, Agartz I, Andreassen OA, Melle I. Depression and depressive symptoms in first episode psychosis. J Nerv Ment Dis. 2010; 198: 67-71.
42. Dai J, Du X, Yin G, Zhang Y, Xia H, Li X, Cassidy R, Tong Q, Chen D, Teixeira AL, Zheng Y, Ning Y, Soares JC, He M, Zhang XY. Prevalence, demographic, and clinical features of comorbid depressive symptoms in drug naïve patients with schizophrenia presenting with first episode psychosis. Schizophr Res. 2018; 193: 182-187.
43. Kucharska J. Sex differences in the appraisal of traumatic events and psychopathology. Psychological Trauma Theory Res Pract Policy. 2017; 9: 575-582.
44. Raballo A, Poletti M. Advances in early identification of children and adolescents at risk for psychiatric illness. Curr Opin Psychiatry. 2020; 33: 611-617.
45. Birchwood M, Iqbal Z, Upthegrove R. Psychological pathways to depression in schizophrenia: studies in acute psychosis, post psychotic depression and auditory hallucinations. Eur Arch Psychiatry Clin Neurosci. 2005; 255: 202-212.
46. Minor KS, Friedman-Yakoobian M, Leung Y, Meyer EC, Zimmet SV, Caplan B, Monteleone T, Bryant C, Guyer M, Keshavan MS, Siedman LJ. The impact of premorbid adjustment, neurocognition and depression on social and role functioning in patients in an early psychosis treatment program. Aust N Z J Psychiatry. 2015; 49: 444-452.
47. Chiappelli J, Nugent KL, Thangavelu K, Searcy K, Hong LE. Assessment of trait and state aspects of depression in schizophrenia. Schizophr Bull. 2014; 40: 132-142.
48. Addington .D, Addington J, Schissel, B. A depression rating scale for schizophrenics. Schizophr Res. 1990; 3: 247-251.
49. Pelizza L, Poletti M, Azzali S, Paterlini F, Garlassi S, Scazza I, Chiri LR, Pupo S, Pompili M, Raballo A. Suicide risk in young people at Ultra-High Risk (UHR) of psychosis: findings from a 2-year longitudinal study. Schizophr Res. 2020d; 220: 98-105.
50. Pelizza L, Leuci E, Quattrone E, Paulillo G, Azzali S, Pupo S, Pellegrini P. Depressed Mood in first episode schizophrenia: findings from a 1-year follow-up in an Italian real-world care setting. Psychiatry. 2022; 23: 1-3. https://doi.org/10.1080/00332747.2022.2120308.
51. Pelizza L, Quattrone E, Leuci E, Paulillo G, Azzali S, Pupo S, Pellegrini P. Anxious-depressive symptoms after a first episode of schizophrenia: response to treatment and psychopathological considerations from the 2-year "Parma Early Psychosis" program. Psychiatry Res. 2022; 317: 114887. https://doi.org/10.1016/j.psychres.2022.114887.