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Original article

Depressed mood in first episode psychosis: findings from the "Parma-Early Psychosis" program

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SUMMARY

Objective

Depressed mood (DM) is relatively frequent in psychosis and significantly associated with suicidal behavior and poorer prognosis. However, it is often under-recognized and under-treated, especially at the illness onset. The aims of this research were: (1) to longitudinally assess DM levels in young subjects with First Episode Psychosis (FEP) over a 2-year follow-up period, and (2) to explore any relevant association of DM with clinical features and the specialized intervention components of an Italian "Early Intervention in Psychosis" (EIP) program, both at baseline and along the follow-up.

Methods

The Positive And Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF) were completed by 266 FEP individuals (aged 12-53 years). Regression analyses with DM as the dependent measure and sociodemographic, psychopathological and treatment characteristics as independent parameters were also performed (both at baseline and along the follow-up).

Results

Relevant DM (i.e. PANSS "Depression" item subscore of ≥ 5) descreased over time and showed longitudinally stable associations with PANSS "Negative Symptoms" and "Positive Symptoms" scores. Along the follow-up, reduction in DM levels was also related to higher antidepressant dose at entry and lower antipsychotic dose prescribed at the end of our research (i.e. after 24 months of follow-up).

Conclusions

Relevant DM is experienced in FEP and in the first specialist contact within specialized EIP programs. However, DM severity levels tends to decrease overtime, together with general improvments in psychosis psychopathology and with antidepressant prescription at entry.

Key words: depression, early intervention in psychosis, first episode psychosis, treatment response, follow-up

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Introduction

Depressed Mood (DM) is relatively common in First Episode Psychosis (FEP). It occurs in its prodromal stage, during the acute phase or may follow the course of positive symptoms in the post-acute period [1,2]. About this, a 35-45% baseline prevalence of clinical depression was reported in FEP populations [3], where it significantly contributes to increase the risk for psychotic relapse and to induce poor real-world performance and bad quality of life [4]. Furthermore, it has been reported that DM is one of the

major predictors for suicidal ideation in FEP, even more than command hallucinations [5]. Early identification and timely intervention on DM in FEP should therefore be considered as a crucial clinical strategy for suicide prevention and for prognosis improvement [6].

Although quite common, DM in FEP is overall *neglected*, especially in its treatment correlates, mainly due to the clinical emphasis on treating positive and negative symptoms of psychosis [7]. Specifically, knowledge is particularly limited on the role of DM on treatment response [8] and discharge outcomes of FEP people enrolled into "Early Intervention in Psychosis" (EIP) protocols [9].

Starting from this background, the *aims* of this research were:

1. to investigate the baseline prevalence rate of FEP patients with relevant DM and to compare their sociodemographic and clinical features with FEP subjects without relevant DM;
2. to longitudinally monitor the course of DM in the FEP total group along a 2-year follow-up period within a specialized EIP protocol;
3. to explore the associations of DM with sociodemographic characteristics, clinical data and the specific EIP treatment components both at baseline and across 24 months of follow-up.

No Italian investigation specifically examining the longitudinal course of DM in FEP and its treatment response to specialized EIP intervention components has been published in the literature to date.

Materials and methods

Setting and sample

Participants were recruited between January 2013 and June 2019 within the "Parma-Early Psychosis" (*Pr-EP*) program, a specialized EIP program specifically implemented in all adult and adolescent mental health services of the Parma Department of Mental Health [10].

Inclusion criteria were: (1) mental health help-seeking request; (2) age 12-35 years; (3) FEP within one of the following DSM-IV-TR diagnoses [11]: schizophrenia, schizophreniform disorder, brief psychotic disorder, schizoaffective disorder, delusional disorder, affective (bipolar or major depressive) psychosis or psychotic disorder not otherwise specified; and (4) a DUP ("Duration of Untreated Psychosis") of < 2 years. This DUP length was specifically selected because it is the usual limit to provide specialized interventions within the EIP paradigm [12].

Exclusion criteria were: (1) past antipsychotic intake or current antipsychotic intake for more than 2 months; (2) past full-blown psychotic episode within a DSM-IV-TR diagnosis of both affective and non-affective psychosis; (3) current substance dependence as defined in the DSM-IV-TR criteria [11]; (4) neurological disorder or any other medical condition associated with psychiatric symptoms; and (5) known intelligence quotient < 70. Specifically, we considered past antipsychotic intake (i.e. in previous illness episodes and prior to the Pr-EP enrollment) as a functional equivalent of a past psychotic episode, in line with the definition of psychosis threshold proposed by Yung and co-workers [13] within their EIP paradigm (i.e. "essentially that at which antipsychotic medication would probably be started in the common clinical practice").

All participants (and their parents, if minors) gave their written informed consent prior to their inclusion in this study. Local ethical approvals were obtained for the research (AVEN protocol n. 36102/09.09.2019). This research was also conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Measures

The clinical evaluation of this investigation included the Positive And Negative Syndrome Scale (PANSS) [14] and the Global Assessment of Functioning (GAF) scale [11]. Trained Pr-EP team members completed such instruments at entry and every year during the follow-up. Regular supervision sessions assured their inter-rater reliability [15].

The *PANSS* is commonly used to evaluate psychopathology in psychosis. In the present research, we considered a PANSS "Depression" (G6) item subscore of ≥ 5 (i.e. at least "a distinctly depressed mood associated with obvious sadness, pessimism, loss of social interest, psychomotor retardation and interference in sleep and appetite") [14] as a clinical index of relevant DM. Moreover, as proposed by Shafer and Dazzi [16], we also considered the following 4 main dimensions in the "core" psychopathology of psychosis: "Positive Symptoms", "Negative Symptoms", "Disorganization" and "Resistance/Activation". The Italian version of the PANSS has been widely used also in young subjects with FEP [17].

The *GAF* is commonly used to evaluate socio-occupational functioning in psychosis. The Italian version of the GAF has been frequently administered also in young individuals with FEP [18].

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*) [19]. According to their symptom severity, FEP individuals were then provided with a 2-year comprehensive intervention protocol including psychopharmacological therapy and a multicomponent psychosocial treatment (combining an intensive recovery-oriented case management, psy-

choeducational sessions for family members and an individual psychotherapy mainly based on cognitive-behavioral modules) [20], as suggested by the current guidelines on the topic [21].
Low-dose atypical *antipsychotic* medication was used as first-line pharmacological therapy [22]. According to the "Defined Daily Doses" method [23], the daily dose of different antipsychotics was reported and standardized as equivalent dose of chlorpromazine (mg/die). As for *antidepressants*, we used a method suggested in a recent meta-analysis on dose equivalence of antidepressant medications, which were standardized and reported as equivalent dose of fluoxetine [mg/day]) [24].
In accordance with the modules proposed by Fowler and colleagues [25], *individual psychotherapy* sessions were also addressed on treating clinical depression, suicide risk, anxiety and distress. Ten meetings (each lasting 1 hour) were offered in the first year of treatment. Booster sessions were also provided in case of specific symptoms of psychotic relapse [26].
In line with the model developed by Kuipers and coworkers [27], *psychoeducational* sessions for family members included problem-solving, communication and support techniques. Eight meetings were offered to each family in the first 6 months of treatment. Booster sessions were provided in case of functioning decline and/or critical family relationships [28].
Case management was aimed at promoting early recovery and at preventing long-term disability [29]. Two sessions per month (each lasting 1 hour) were provided in the first year of treatment. Monthly booster sessions were also offered in case of specific functioning needs [30].
Individuals having a baseline PANSS "Depression" item subscore of ≥ 5 were classified as FEP patients with relevant DM (FES/DM+). The remaining participants were considered as not having a relevant DM at entry and were included in the FES/DM- subgroup.

Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS) for Windows, version 15.0 [31]. All tests were two-tailed with a significance level set at 0.05. In inter-group comparisons, the Mann-Whitney U test was used to examine quantitative parameters, while the Chi-square (χ^2) test was performed to assess qualitative variables. The Wilcoxon test for repeated measures was used in the FEP total sample to investigate the longitudinal stability of DM severity levels during the 2-year follow-up period.
A binary logistic regression analysis with the dichotomized PANSS "Depression" item score (cut-off score of ≥ 5) as the dependent parameter and clinical and sociodemographic features as independent parameters was performed at entry in the FEP total group. Moreover, a linear regression analysis with PANSS "Depression" item score as the dependent measure and Pr-EP treatment components, clinical and sociodemographic characteristics as independent parameters was also conducted in the FEP total sample across the 2-year follow-up period. In our longitudinal analyses, we specifically considered the differences (deltas [Δ]) between PANSS scores at baseline (T0) and at the 2-year assessment time (T2) as primary clinical parameters to examine over time. Indeed, in line with what was suggested by Ver Hoef [32], the delta scores better describe the temporal dynamics and longitudinal changes of psychosis psychopathology in comparison with T0 and T2 single measures.

TABLE I. *Sociodemographic data and clinical features of the FEP total sample (n = 266).*

Variable	
Age at entry (in years)	24.00 (20.00-30.00)
Gender (males)	165 (62.0%)
Education (in years)	13.00 (10.00-13.00)
Ethnic group (white Caucasians)	225 (84.6%)
DUP (in months)	6.00 (2.00-13.00)
T0 PANSS "Depression" item subscore	4.00 (2.00-5.00)
T1 PANSS "Depression" item subscore	2.00 (1.00-3.00)
T2 PANSS "Depression" item subscore	2.00 (1.00-2.00)

FEP: first episode psychosis; DUP: duration of untreated psychosis; PANSS: Positive And Negative Syndrome Scale. Frequencies (and percentages) and median (and interquartile range) are reported.

Results

Two hundred and sixty-six FEP patients were recruited for this research. Their sociodemographic and clinical features are shown in the Table I. The baseline DSM-IV-TR axis I diagnoses were: schizophrenia (n = 117; 44.0%), affective psychosis (n = 74; 27.8%), psychotic disorder not otherwise specified (n = 25; 9.4%), brief psychotic disorder (n = 17; 6.4%), schizophreniform disorder (n = 15; 5.6%), schizoaffective disorder (n = 10; 3.7%) and delusional disorder (n = 8; 3.1%). Antidepressant prescription rate at entry was 20.3% (n = 54).

Baseline evaluation

At baseline (T0), 82 (30.8%) FEP participants had a baseline PANSS "Depression" item subscore of ≥ 5 and were included in the FEP/DM+ subgroup (Tab. II). Only 21 (25.6%) of them were taking an antidepressant drug at entry. Compared to FEP/DM-, FEP/DM+ participants showed a younger age, higher PANSS "Positive Symptoms" and "Negative Symptoms" factor subscores and a lower GAF score.
Moreover, a baseline PANSS "Depression" item cut-off score of ≥ 5 (i.e. the presence of a relevant DM at entry)

TABLE II. *Sociodemographic data and clinical features of the FEP total group and the two subgroups.*

Variable	FEP total group (n = 266)	FEP/DM+ (n = 82)	FEP/DM- (n = 184)	X^2/z
Gender (females)	165 (62.0%)	50 (61.0%)	115 (62.5%)	0.056
Ethnic group (white Caucasians)	225 (84.6%)	69 (84.1%)	156 (84.8%)	0.018
Age at entry (in years)	25.72 ± 7.69	24.07 ± 6.92	26.45 ± 7.92	**-2.286****
Education (in years)	15.68 ± 6.04	12.06 ± 2.72	17.33 ± 6.63	-0.216
DUP (in months)	9.01 ± 7.74	10.08 ± 8.49	8.53. ± 7.36	-0.947
DSM-IV-TR diagnosis				
Schizophrenia spectrum disorder	150 (56.4%)	43 (52.4%)	107 (58.2%)	0.753
Affective psychosis	74 (27.8%)	22 (26.8%)	52 (28.3%)	0.058
Brief psychotic disorder	8 (3.0%)	3 (3.7%)	5 (2.7%)	0.172
Psychotic disorder not otherwise specified	34 (12.8%)	14 (17.1%)	20 (10.9%)	1.958
T0 PANSS "Positive Symptoms" factor score	17.33 ± 6.06	19.57 ± 5.68	16.33 ± 5.97	**-4.174***
T0 PANSS "Negative Symptoms" factor score	25.12 ± 9.44	26.98 ± 8.46	24.29 ± 9.75	**-2.007****
T0 PANSS "Disorganization" factor score	22.22 ± 8.47	22.21 ± 7.62	22.23 ± 8.84	-0.096
T0 PANSS "Activation/Resistance" factor score	8.71 ± 4.20	8.10 ± 3.49	8.98 ± 4.47	-1.248
T0 GAF score	44.61 ± 11.24	39.66 ± 11.13	46.86 ± 10.58	**-4.737***
T0 equivalent dose of chlorpromazine (mg/day)	198.00 ± 167.64	222.00 ± 214.38	187.80 ± 141.37	-0.612
T0 equivalent dose of fluoxetine (mg/day)	13.68 ± 39.72	23.53 ± 55.74	9.29 ± 29.09	-1.681
T0 antipsychotic prescription rate	237 (89.1%)	71 (86.6%)	166 (90.2%)	0.770
T0 antidepressant prescription rate	54 (20.3%)	21 (25.6%)	33 (17.9%)	2.065

*FEP: first episode psychosis; FEP/DM+: FEP patients with relevant Depressed Mood ([DM] = PANSS "Depression" item cut-off score ≥ 5); FEP/DM-: FEP patients without relevant DM; DUP: duration of untreated psychosis; DSM-IV-TR: Diagnostic and statistical manual for mental disorders, IV Edition, text revised; PANSS: Positive And Negative Syndrome Scale; GAF: global assessment of functioning; T0: baseline assessment. Frequencies (and percentages), mean ± standard deviation, Chi-square test (X^2) and Mann-Whitney test (z) values are reported. *p < 0.001; **p < 0.5. Statistically significant results are in bold.*

was significantly predicted by higher T0 PANSS "Positive Symptoms" and "Negative Symptoms" factor subscores, as well as lower T0 GAF score (Tab. III). The overall percentage of dichotomized ascription using this model for predicting relevant baseline DM levels in our FEP patients was 75.2%. No association with sociodemographic data was found.

Follow-up evaluation

All FEP subjects ended the 2-year follow-up period. At the *T1 assessment*, antidepressant medication was still prescribed to 49 (18.4%) FEP individuals, with a median equivalent dose of fluoxetine equal to 30.00 mg/day (Interquartile Range [IR] = 20.00-80.00 mg/die). Only 7 (2.6%) FEP participants had a T1 PANSS "Depression" item cut-off score of ≥ 5, with a T1 incidence rate of new cases with relevant DM of 1.5% (n = 4).

At the end of our follow-up (*T2 assessment*), the median of case management sessions was 30 (IR = 16-50), the median of individual psychotherapy sessions was 21 (IR = 12-30) and the median of psychoeducational sessions for family members was 8 (IR = 3-13). Antidepressants were still prescribed to 64 (24.1%) FEP subjects, with a median equivalent dose of fluoxetine of 20.00 mg/day (IR = 20.00-50.00 mg/die). Only 5 (1.9%) FEP individuals had a T2 PANSS "Depression" item cut-off score of ≥ 5, with a T2 incidence rate of new cases with relevant DM of 0.75% (n = 2). Over the 2-years of follow-up, we therefore observed 6 new FEP/DM+ cases for an overall incidence rate equal to 2.25%.

Along the follow-up, a significant decrease in PANSS "Depression" item subscores was found (Tab. IV). Our linear regression analysis results showed that the delta reduction between T0 and T2 PANSS "Depression" item subscores was significantly predicted by higher T0 equivalent dose of fluoxetine, lower T2 equivalent dose of chlorpromazine and delta reductions between T0 and T2 PANSS "Positive Symptoms" and "Negative Symptoms" factor scores.

Discussion

In the current study, *1/3* of FEP patients had a *relevant DM* at entry (i.e. an at least "moderate severe" PANSS "Depression" item subscore = "a distinctly depressed mood associated with pessimism, obvious sadness, loss of social interest, psychomotor retardation and interference in appetite and sleep) [14]. This result is substantially in line with what (35-45%) was reported in the current

TABLE III. *Binary logistic regression results of the dichotomized PANSS "Depression" item score (cut-off ≥ 5) by sociodemographic data and clinical features within the FEP total sample (n = 266) at baseline.*

Variable	B	SE	Wald	df	p	OR	95% CI for OR(B) Lower	upper
Gender (males)	-0.109	0.313	0.120	1	0.729	1.115	-2.060	-0.603
Age at entry (in years)	-0.031	0.022	2.068	1	0.150	1.032	-1.076	-0.989
Education (in years)	-0.001	0.008	0.034	1	0.855	1.001	-1.016	-0.987
Ethnic group (white Caucasians)	0.028	0.418	0.004	1	0.947	0.973	0.429	2.205
DUP (in months)	0.023	0.019	1.449	1	0.229	0.977	0.941	1.015
T0 PANSS "Positive Symptoms" factor score	0.103	0.030	11.566	1	**0.001**	0.902	0.850	0.957
T0 PANSS "Negative Symptoms" factor score	0.049	0.023	4.740	1	**0.029**	0.952	0.910	0.995
T0 PANSS "Disorganization" factor score	-0.045	0.026	3.084	1	0.079	1.046	-1.100	-0.995
T0 PANSS "Activation/Resistance" factor score	-0.119	0.043	7.682	1	0.076	1.126	-1.225	-1.035
T0 GAF score	-0.044	0.015	8.215	1	**0.004**	1.044	-1.076	-1.014
Constant	0.658	1.234	0.284	1	0.594	0.518	-	-
Overall model fit test → X^2 = 49.923; p = 0.0001 Associated strength → Cox–Snell R^2 = 0.172, Negelkelke R^2 = 0.247								

FEP: first episode psychosis; DUP: duration of untreated psychosis; PANSS: Positive And Negative Syndrome Scale; GAF: global assessment of functioning; T0: baseline assessment; 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; X^2: Chi-square value; R^2: R-square or coefficient of determination; p: statistical significance; p-value lower than 0.05 are reported as bold values.

TABLE IV. *PANSS "Depression" item scores and their associations with sociodemographic data, relevant clinical features and the specialized intervention components of the Pr-EP program across the 2-year follow-up period in the FEP total sample (n = 266).*

Variable	T0	T1	T2	z (T0-T1)	z (T0-T2)	z (T1-T2)
PANSS "Depression" item score	4 (2-5)	2 (1-3)	2 (1-2)	**-9.736***	**-8.657***	**-3.578***

T0-T2 Delta PANSS "Depression" item scores	B	SE	95% CI for B Lower	Upper	β	p	
Constant							R^2 = 0.341
Gender (females)	0.260	0.871	-1.462	1.983	-	0.765	$F_{[df=20]}$ = 2.901
Age at entry (in years)	0.205	0.255	-0.299	0.709	0.630	0.423	**p = 0.0001**
Education (in years)	-0.014	0.017	-0.047	0.019	-0.065	0.406	
Ethnic group (non-white Caucasians)	-0.003	0.002	-0.006	0.000	-0.124	0.100	
DUP (in months)	0.162	0.315	-0.461	0.785	0.039	0.608	
T0 equivalent dose of Chlorpromazine (mg/day)	0.031	0.017	-0.003	0.064	0.141	0.070	
T1 equivalent dose of Chlorpromazine (mg/day)	0.003	0.044	-0.083	0.090	0.006	0.939	
T2 equivalent dose of Chlorpromazine (mg/day)	0.002	0.004	-0.005	0.010	0.042	0.581	
T0 equivalent dose of Fluoxetine (mg/day)	-0.030	0.014	-0.059	-0.002	-0.159	**0.039**	
T1 equivalent dose of Fluoxetine (mg/day)	0.011	0.005	0.001	0.022	0.186	**0.035**	
T2 equivalent dose of Fluoxetine (mg/day)	0.000	0.004	-0.008	0.009	0.011	0.905	
T2 number of individual psychotherapy sessions	0.006	0.004	-0.001	0.013	0.139	0.097	
T2 number of psychoeducational sessions for family members	-0.008	0.010	-0.028	0.012	-0.067	0.418	
T2 number of case management sessions	0.024	0.017	-0.010	0.059	0.123	0.158	
T0-T2 Delta "Positive Symptoms" factor scores	-0.002	0.004	-0.009	0.006	-0.035	0.678	
T0-T2 Delta "Negative Symptoms" factor scores	0.055	0.027	0.002	0.108	0.188	**0.040**	
T0-T2 Delta "Disorganization" factor scores	0.053	0.020	0.012	0.093	0.288	**0.011**	
T0-T2 Delta "Excitement/Resistance" factor scores	-0.009	0.025	-0.059	0.040	-0.044	0.709	
T0-T2 Delta GAF scores	-0.039	0.034	-0.106	0.029	-0.104	0.258	
	-0.003	0.010	-0.024	0.017	-0.028	0.734	

PANSS: Positive And Negative Syndrome Scale; Pr-EP: Parma-Early Psychosis; FEP: first episode psychosis; T0: baseline; T1: 1-year assessment time; T2: 2-year assessment time; DUP: duration of untreated psychosis; 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; R^2: R-square or coefficient of determination; F: statistic test value for linear regression; df: degrees of freedom. Median (and interquartile range) and Wilcoxon test (z) values are also reported. Statistically significant p values are in bold.

literature [3,33,34], supporting that a quite relevant proportion of FEP patients may show a clinically significant DM already at the enrollment within EIP services [35]. DM in FEP is therefore sometimes relevant enough to justify early identification and a timely targeted intervention [36]. About this, Griffiths and colleagues [37] considered depression in FEP as an *early clinical feature* in the developmental trajectory of psychosis psychopathology and as a central psychopathological characteristic in the clinical network maps of psychotic symptoms, both at baseline and over time. According to these authors, effective treatments on DM could have the potential to lead to a better recovery and to global symptom improvements.

However, we observed a baseline *antidepressant prescription* rate of only 20% (25% in the FEP/DM+ subgroup). These findings further support that DM may be often under-recognized and under-treated in FEP individuals [38], probably due to the clinical emphasis given at treating positive and negative symptoms of psychosis. These results are also in line with what was observed by Herniman and co-workers [34] in a recent meta-analysis on comorbid depressive features in subjects with first-episode schizophrenia spectrum disorders, reporting no significant link between antidepressant therapy and prevalence of clinically relevant depressive symptoms. Additionally, in a longitudinal study on concomitants of depression in first episode schizophrenia, Phahladira and co-workers [39] found only a 5% prescription rate of antidepressant drugs at baseline.

Clinical suggestions

The results of this investigation showed a significant association of DM in FEP and *positive symptom* severity levels, both at baseline and as longitudinal changes in scores along the 2 years of follow-up. According to Phahladira and co-workers [39], the psychopathological link between depressive and positive dimensions at the psychosis onset could be particularly important at a "symptom-level", reflecting state-related fluctuations in positive symptoms. This is also in line with the intrinsic hypothesis of depression in psychosis, hypothesizing that DM could partly follow the development of positive symptoms [34].

Furthermore, DM in FEP patients was significantly associated also with *negative symptom* severity levels, both at entry and as longitudinal changes in scores across the follow-up. As depressive and negative symptoms are often hard to differentiate from one another in FEP, we can't ascribe a clear causality to these simple quantitative relationships, which could be partly related to their phenomenological overlap [40] and/or to secondary negative symptoms as consequences of clinically relevant depressed mood [20].

Given the longitudinal stability of associations of DM with positive and negative dimensions of early psychosis, mood depression in FEP could also be potentially considered as a *stable index of psychopathological severity* overtime. In this respect, Birchwood and colleagues [41] suggested that DM could develop in early psychosis due to the intrinsic illness process and/or negative cognitive appraisals of the experience and meaning of psychotic disorder. Indeed, the disruption that FEP can have on patients' interpersonal relationships, on their vocational goals and their identity construction could be particularly unfavorable during the critical developmental phase of adolescence and/or young adulthood [42].

The findings of this research also showed a relevant association between *functioning decline* and DM at baseline. Previous results on this topic was substantially mixed, with some investigations suggesting poor daily functioning in FEP patients with clinically relevant depression [43], and others observing no relationship [44,45]. Such inconsistent findings could be due to third parameters that may mediate this association (e.g. personality traits, neurocognitive factors, developmental trajectory).

Finally, we found a significant association between DM and *younger age* at entry. This seems to further support that the negative impact of FEP onset during adolescence or young adulthood could have a "pathoplastic" role for the development of relevant DM at the psychosis onset, which may also subsequently contribute to induce poorer real-world performance and to increase suicidal risk [5].

Treatment response

The findings of this study showed a significant *decrease in DM* during the 2 years of our follow-up. This supports the results reported by Phahladira and co-workers [39], who observed that depressive symptoms in patients with first episode schizophrenia were greatest at baseline, with the most significant reduction during the first 3 months of intervention and improvement maintenance along the 2 years of their follow-up period. Furthermore, considering all the duration of our follow-up, we found exclusively 6 new FEP/DM+ cases [4 (66.7%) of them in the first 12 months], with a cumulative incidence rate of "de novo" DM in FEP equal to only 2.25%. Overall considered, our findings support a relevant decrement of DM severity levels in FEP patients treated within specialized EIP programs. In the current research, this decrease was positively associated with the equivalent dose of antidepressant medication prescribed at baseline and with longitudinal reductions in positive and negative symptom severity observed over the follow-up, as well as negatively related with the equivalent dose of antipsychotic drug still prescribed at the end of the investigation (T2 assessment).

Our evidence on negative association between longitudinal decrease in DM and T2 *antipsychotic* dosage

could suggest a potential, direct "depressogenic effect" of antipsychotic medications [39]. About this, a lack of improvement in positive symptoms overtime could induce clinicians in increasing the prescribed dose of antipsychotics, resulting in a vicious circle potentially worsening comorbid DM in FEP patients.
Finally, we observed that the baseline prescription of an *antidepressant* drug was related to significant improvements in DM severity levels at the end of our study. This is not concordant with what was reported in the current literature [46,47], overall suggesting no association between longitudinal severity in clinical depression and prescription of antidepressants in early psychosis. However, in a recent meta-analysis on antidepressants in individuals at Clinical High Risk (CHR) for psychosis, Raballo and colleagues [48] suggested that ongoing antidepressant exposure at inception in CHR subjects was associated to a reduced risk of transition to psychotic disorder at follow-up. Thus, future research in larger FEP populations to confirm our promising results is needed.

Limitations

A first weakness of this research is associated to sample characteristics. Indeed, we investigated FEP patients in a "real-world" care setting, primarily aimed at offering specialized EIP interventions within community mental health services. Our findings therefore may be exclusively compared to similar clinical populations. Moreover, even if a strength of this study was the recruitment of patients at the onset of psychosis, our findings cannot be generalized to patients at different illenss phases (such as those with a prolonged psychotic disorder).
Furthermore, the current research was designed within an EIP program not specifically focused on DM in FEP. Specifically, psychopathology was assessed with the PANSS, an instrument widely administered in FEP populations, but poorly articulated for measuring depression. Therefore, future studies exploring DM with more specific instruments for psychosis [e.g. the Calgary Depression Scale for Schizophrenia (CDSS)] [49] are needed. However, given the common application of the PANSS in FEP patients, our research has the potential to be replicated in similar samples. This is of primary importance since investigations exploring treatment response of EIP protocols on DM at the psychosis onset are still poor and depression is commonly associated with negative long-term outcomes and suicide risk.
Finally, our treatment parameters were not randomly attributed. This restricts our ability to derive causal conclusion on the reported longitudinal associations with changes in DM severity levels. Indeed, these correlations could also depend on other plausible explanations (e.g. FEP patients with more severe psychopathology could get more intensive treatments and improve the most, partially because they had the most to improve).

Conclusions

DM is quite relevant in FEP, where it could be considered not exclusively as a superimposed comorbidity, but also as an inextricable clinical dimension of the disorder [50]. An in-depth assessment of comorbid depression is therefore crucial at the first presentation of FEP individuals within EIP services, especially in order to prevent suicide and to improve long-term outcomes. The findings of this study showed a longitudinal improvement in DM severity levels, which was significantly associated with higher antidepressant dose at baseline, lower antipsychotic dosage still taken at T2 assessment and longitudinal reductions in positive and negative symptoms across the 2 years of follow-up. An antidepressant therapy in FEP subjects with clinically relevant DM is thus recommended.

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Conflict of interest statement

The Authors declare no conflict of interest.

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Author contributions

LP, E: study conceptualization and design; SP: literature search; LP, EL, EQ, SA: data colection and curation; LP: formal analyses; LP: wrote the first draft of the manuscript; all Authors: reviewed and approved the final version of the manuscript.

Ethical consideration

This study was approved by AVEN Institutional Ethics Committee (n. 36102/09.09.2019).
The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.
Written informed consent was obtained from each participant/patient for study participation and data publication.

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