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RESEARCH PAPER

DEPRESSIVE FEATURES IN INDIVIDUALS WITH FIRST EPISODE PSYCHOSIS: PSYCHOPATHOLOGICAL AND TREATMENT CONSIDERATIONS FROM A 2-YEAR FOLLOW-UP STUDY

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Abstract

Objective: Comorbid depression is quite common in early psychosis and specifically related to suicidal behavior and poor long-term outcomes. However, Depressive Symptoms (DS) are often neglected in both research and treatment, especially at the psychosis onset. The goals of this investigation were: (a) to longitudinally explore DS levels in patients with First Episode Psychosis (FEP) during 24 months of follow-up, and (b) to investigate the associations of DS with psychopathology and intervention components of an "Early Intervention in Psychosis" (EIP) program across the follow-up period.

Method: The Global Assessment of Functioning (GAF) and the Positive And Negative Syndrome Scale (PANSS) were completed by 266 FEP subjects. A linear regression analysis with DS as the dependent parameter and psychopathological and treatment characteristics as independent variables was performed (both at baseline and across the follow-up period).

Results: DS had enduring associations with PANSS "Positive Symptoms" and "Negative Symptoms" subscores. During the investigation, FEP subjects significantly improved their DS severity levels. This was related to the number of individual psychotherapy meetings supplied within the EIP protocol, as well as to a higher antidepressant dose and a lower antipsychotic dose prescribed during the follow-up.

Conclusions: DS are quite prominent in FEP, even at the recruitment time in EIP services. Nevertheless, DS severity tends to diminish overtime, especially with the provision of specialized EIP treatments.

Key words: depression, early intervention in psychosis, first episode psychosis, psychotherapy, treatment response

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Introduction

Depressive Symptoms (DS) are relatively frequent in First Episode Psychosis (FEP) and can occur during any phase of the psychotic illness (i.e. in the prodromes, during its acute stage or -during the course of positive symptomatology in the post-acute period) (Romm et al., 2010; Pelizza et al., 2021a; Bodoano Sanchez et al., 2022). Specifically, a 35-50% baseline prevalence of depressive psychopathology in FEP was reported (Sonmez et al., 2013; Basu et al., 2020). DS in FEP significantly contribute to increased risk of psychotic relapse, low remission rate, poor daily functioning and self-harm (da Silva et al., 2021; Vila-Badia et al., 2022). In particular, it has also been reported that DS are one of the most relevant predictors of suicidal behavior in FEP, even more than positive symptoms (such as command hallucinations) (Pelizza et al., 2020a). So, early detection and intervention of DS in FEP should be implemented as a crucial clinical strategy for suicide prevention and for improving long-term prognosis (Pelizza et al., 2021b).

However, although frequent, DS are still often *underestimated* in both research and treatment, mainly due to the emphasis on positive and negative symptoms, and to the doubts surrounding their clinical significance and etiology (Ferraro et al., 2021). In particular, knowledge is limited on functional, clinical and sociodemographic correlates of DS in FEP (Coentre et al., 2017), and on the influence of DS on treatment response and discharge outcomes of FEP individuals recruited within "Early Intervention in Psychosis" (EIP) services (Landi et al., 2021). In this sense, depressive

psychopathology is a typical example of a crucial, under-recognized intervention target in FEP, which could have the potential to determine a better recovery and a global symptom improvement (Griffiths et al., 2021).

Thus, the *goals* of this investigation were:

(1) to monitor the longitudinal course of DS in FEP subjects treated within a 2-year Italian EIP protocol;
(2) to explore associations of DS with clinical features, sociodemographic data and the EIP intervention components during the follow-up.

No Italian research assessing the course of DS over time and their treatment response in people with FEP has been published in the literature to date.

Materials and methods

Patients

Individuals were enlisted between January 2013 and June 2019 within the "Parma-Early Psychosis" (*Pr-EP*) program, i.e. an evidence-based, recovery-oriented EIP protocol specifically planned in all community adult and adolescent mental health centers of the Parma Department of Mental Health (in Italy) (Leuci et al., 2022).

Inclusion criteria included: (1) mental health help-seekers; (2) 12-35 years old; (3) FEP within the following DSM-IV-TR diagnoses: schizophreniform disorder, brief psychotic disorder, schizoaffective disorder, schizophrenia, delusional disorder, affective (major depressive or bipolar) psychosis or psychotic disorder not otherwise specified (APA, 2000); and (4) a DUP ("Duration of Untreated Psychosis" = the time period [in months] between the onset of overt psychotic features and the first antipsychotic intake) (Woods et al., 2020) of < two years. This DUP extent was chosen because it is considered the usual limit to offer effective, specialized interventions within the EIP paradigm (Raballo & Poletti, 2020).

Exclusion criteria included: (1) any past antipsychotic intake or current (first) antipsychotic intake –of more than 60 days; (2) previous overt psychotic features within DSM-IV-TR diagnoses of both affective and non-affective psychosis; (3) current substance dependence (as defined in the DSM-IV-TR criteria); (4) neurological disorder or any other somatic disease with psychiatric symptoms; and (5) known intelligence quotient < 70. We considered previous antipsychotic intake (i.e. in past episodes of the disorder and thus previously to the Pr-EP recruitment) as a functional equivalent of a past psychotic episode, in line with what was proposed by Yung et al. (2005) on the diagnostic threshold of psychosis within the EIP paradigm, which was defined as essentially that at which an antipsychotic drug would likely be prescribed in the common clinical practice.

All participants (and their parents/tutors, if minors) provided their written informed consent before their enrollment in this investigation. Ethical approvals were locally acquired for the research (AVEN protocol n. 36102/09.09.2019). This study was performed according to the ethical standards of the 1964 Declaration of Helsinki and its later revisions.

Instruments

The psychopathological assessment included the Global Assessment of Functioning (GAF) scale (APA, 2000) and the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987). Trained Pr-EP team members completed those instruments at entry and every 12 months during the follow-up. Supervision meetings ensured the inter-rater reliability (Leuci et al., 2022). A *clinical and sociodemographic chart* (including information on DUP and delivery intensity of the Pr-EP treatment components) was also filled in at baseline (Pelizza et al., 2021c).

The *PANSS* is commonly used to assess the clinical severity of psychopathology in early psychosis (Pelizza et al., 2020b). As proposed in the meta-analysis by Shafer and Dazzi (2019) on the PANSS factor configuration, we considered five main dimensions: "Negative Symptoms", "Positive Symptoms", "Affect" (Depression), "Disorganization" and "Resistance/Activation-". The PANSS "Affect" factor was composed of five items: G6 "Depression", G3 "Guilt Feelings", G4 "Tension", G2 "Anxiety" and G1 "Somatic Concern-". The Italian version of the PANSS was widely used also in individuals with FEP (Pelizza et al., 2021d).

The *GAF* is widely completed to assess socio-occupational and clinical functioning in people with severe mental illness. The Italian version of the GAF was commonly used also in young people with FEP (Pelizza et al., 2022a).

Procedures

The Structured Clinical Interview for DSM-IV-TR axis I disorders (*SCID-I*) (First et al., 2002) was administered by trained Pr-EP team members to formulate the axis-I diagnosis. FEP patients were then recruited within the Pr-EP program usually within three weeks (Pelizza et al., 2020c). Based on their symptom levels, a 2-year comprehensive treatment protocol, including psychopharmacological therapy and a multifaceted psychosocial treatment (combining intensive case management oriented to early recovery, psychoeducation for family members and individual psychotherapy inspired by cognitive-behavioral principles), was provided to each FEP subject, as indicated in the modern guidelines on the EIP paradigm (NICE, 2016).

A -low-dose atypical *antipsychotic* drug was used as first-line pharmacological therapy (Barnes et al., 2020). In accordance with the "Defined Daily Doses" method (Leucht et al., 2016), the daily dosage of different antipsychotics was standardized and reported as an equivalent dose of chlorpromazine (mg/-day). As for *antidepressants*, we referred to a modern method used in a recent meta-analysis on the dose equivalence of antidepressant drugs. In this method, antidepressants were described and standardized as an equivalent dose of fluoxetine [mg/day]) (Furukawa et al., 2019).

According to Fowler et al. (1995), *individual psychotherapy* included psychoeducation on clinical depression, suicide risk, anxiety and psychological distress. Ten meetings (each lasting 1 hour) were supplied in the first year; booster sessions were also provided in case of specific symptoms of psychotic relapse (Pelizza et al., 2022b).

According to Kuipers et al. (2002), *psychoeducational* meetings for family members combined problem-solving, communication and support techniques. Eight meetings - were offered to each family in the first six months; booster sessions were also supplied in case of functioning decline and/or relapse of specific psychotic symptoms (Pelizza et al., 2021e).

Case management was focused on promoting early recovery and preventing long-term disability (Wong et

al., 2019). Two sessions per month (each lasting - one hour) - were supplied in the first 12 months of treatment; monthly booster sessions were also offered according to specific functioning needs (Pelizza et al., 2022c).

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%). The antidepressant

Table 1. *Sociodemographic and clinical characteristics of the FEP 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 "Affect" factor score	16.00 (12.00-20.00)
T1 PANSS "Affect" factor score	10.00 (8.00-13.00)
T2 PANSS "Affect" factor score	9.00 (6.00-12.00)
T0 equivalent dose of Chlorpromazine (mg/day)	180.00 (120.00-140.00)
T0 equivalent dose of Fluoxetine (mg/day)	40.00 (20.00-40.00)
T0 antipsychotic prescription rate	266 (100%)
T0 antidepressant prescription rate	54 (20.3%)

Legend. FEP = First Episode Psychosis; DUP = Duration of Untreated Psychosis; T0 = baseline assessment; T1 = 1-year assessment time; T2 = 2-year assessment time; PANSS = Positive And Negative Syndrome Scale. Frequencies (and percentages) and median (and interquartile range) are reported.

Statistical analysis

The Statistical Package for Social Science (SPSS) for Windows, version 15.0 (SPSS Inc., 2010) was used to examine collected data. All tests were two-tailed. Their significance level was set at 0.05. As for repeated measures, the Wilcoxon test was performed to assess the 2-year longitudinal course of DS in the FEP total group. Linear regression analysis with DS as the dependent measure and Pr-EP intervention factors, clinical characteristics and sociodemographic features as independent measures, was also performed in our FEP population both at baseline and across the 2-year follow-up period. In longitudinal analyses, the differences (deltas [Δ]) between PANSS dimension scores at entry (T0) and at 1- or 2-year assessment time (T1/T2) as primary clinical parameters were specifically examined. - In line with what was suggested by Ver Hoef (2012), the delta scores better define and qualify the temporal dynamics and longitudinal changes of psychotic psychopathology in comparison with T2, T1 and T0 single scores.

Results

266 FEP participants were enrolled for this investigation. - **table 1** shows their clinical and sociodemographic characteristics. In particular, 82 (30.8%) FEP individuals had a baseline PANSS "Depression" item score of ≥ 5 (i.e. -at least "moderately severe" item severity level) (Kay et al., 1987). In accordance with the DSM-IV-TR criteria (APA, 2000), the axis I diagnoses of our FEP participants were represented by schizophrenia (n = 117; 44.0%),

prescription rate at entry was 20.3% (n = 54). All FEP subjects were taking antipsychotics at baseline.

Baseline assessment

At entry, the PANSS "Affect" factor score was significantly predicted by higher PANSS "Positive Symptoms" and "Negative Symptoms" dimension subscores, as well as by a lower GAF score (**table 2**). Specifically, the strongest predictor was represented by the baseline positive symptom severity level. No association with sociodemographic characteristics was found.

Follow-up assessment

All individuals concluded the 2-years of follow-up. At *T1*, the median of case management meetings was 12 (interquartile range [IR] = 5-21), the median of individual psychotherapy meetings was 13 (IR = 9-19) and the median of psychoeducational meetings was 5 (IR = 1-9). Antipsychotic drugs were still taken by 219 (82.3%) FEP participants, with a median equivalent dose of chlorpromazine equal to 150.00 mg/day (IR = 120.00-240.00 mg/- day). Antidepressants were still prescribed to 49 (18.4%) FEP subjects, with a median equivalent dose of fluoxetine equal to 30.00 mg/day (IR = 20.00-80.00 mg/- day).

At *T2*, the median of case management meetings was 30 (IR = 16-50), the median of individual psychotherapy meetings was 21 (IR = 12-30) and the median of psychoeducational meetings was 8 (IR = 3-13). At the end of our follow-up, antipsychotics

Table 2. *Linear regression analysis results of PANSS "Affect" factor score by sociodemographic data and clinical features within the FEP group (n = 266) at baseline*

T0 PANSS "Affect" factor score	B	SE	95% CI for B Lower	Upper	β	p	R^2 = 0.184 $F_{[df=10]}$ = 5.561 **p = 0.0001**
Constant	-.455	0.262	-1.970	-0.940	-	0.000	
Gender (male)	0.022	0.057	-0.089	0.134	0.023	0.693	
Age at entry (in years)	-0.005	0.004	-0.012	0.002	-0.084	0.157	
Education (in years)	2.380	0.000	-0.001	0.001	0.003	0.958	
Ethnic group (white Caucasian)	-0.008	0.076	-0.158	0.141	-0.006	0.913	
DUP (in weeks)	0.004	0.003	-0.003	0.011	0.071	0.223	
PANSS "Positive Symptoms" factor score	0.021	0.005	0.010	0.031	0.262	**0.000**	
PANSS "Negative Symptoms" factor score	0.010	0.004	0.002	0.018	0.196	**0.016**	
PANSS "Disorganization" factor score	-0.009	0.005	-0.018	-0.000	-0.167	0.059	
PANSS "Activation/Resistance" factor score	-0.022	0.008	-0.037	-0.007	-0.201	0.063	
GAF score	-0.008	0.003	-0.013	-0.003	-0.196	**0.002**	

Legend. PANSS = Positive And Negative Syndrome Scale; FEP = First Episode Psychosis; T0 = baseline assessment; 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. Statistically significant p values are in bold.

drugs were still taken by 195 (73.3%) FEP subjects, with a median equivalent dose of chlorpromazine equal to 150.00 mg/day (IR = 90.00-300.00 mg/-day). Antidepressant medications were still prescribed to 64 (24.1%) FEP individuals, with a median equivalent dose of fluoxetine equal to 20.00 mg/day (IR = 20.00-50.00 mg/-day).

Along the 2-year follow-up period, a significant decrease in the PANSS "Affect" factor subscores was observed (**table 3**). Linear regression analysis results showed that the delta decrease between T0 and T1 PANSS "Affect" dimension subscores was predicted by a higher T1 equivalent dose of fluoxetine and higher delta reductions between T0 and T1 PANSS "Positive Symptoms" and "Negative Symptoms" domain scores. Furthermore, the delta reduction between T0 and T2 PANSS "Affect" domain subscores was predicted by a lower T2 equivalent dose of chlorpromazine, a higher T0 equivalent dose of fluoxetine, a higher T2 number of individual psychotherapy meetings and higher delta reductions between T0 and T2 PANSS "Positive Symptoms" and "Negative Symptoms" dimension scores. At both T1 and T2, the strongest predictor of PANSS "Affect" dimension score reduction was represented by the improvement in PANSS "Positive Symptoms" domain score.

Discussion

In the current investigation, approximately - one third of FEP participants showed an at least "moderately severe" PANSS "*Depression*" item score at baseline (i.e., the presence of a distinctly depressed mood associated with pessimism, obvious sadness, psychomotor retardation, loss of social interest and interference in sleep and appetite) (Kay et al., 1987). This finding is slightly lower than those (35-50%) reported in the current literature (Sonmez et al., 2013; Herniman et al., 2019; Basu et al., 2020). However, it substantially confirms that a relevant proportion of FEP subjects suffers from severe depressed mood - at their entry into EIP programs (Pelizza et al., 2019). Thus, DS in FEP are often relevant enough to justify early diagnostic evaluation and timely intervention (Poletti et al., 2021). Moreover, - depressive – characteristics are very common in the prodromal phase of psychosis (Larson et al., 2010) and in young people having an at-risk mental state for psychosis (also in adolescence) (Pelizza et al., 2018)-. They should be clinically noted as having *early comorbid characteristics* in the developmental course of psychotic psychopathology. In this respect, Griffiths et al. (2021) described depression in FEP as a central symptom in clinical network maps both at baseline and over time, which - may have the potential to lead to global symptom improvements.

However, in the present investigation, only a 20% *antidepressant prescription* rate was found at baseline. This supports the results reported by Herniman et al. (2019) in a meta-analysis on depressive psychopathology in first-episode schizophrenia spectrum disorders, suggesting no significant link between antidepressant therapy and prevalence of depressive features. Similarly, in a longitudinal research study on concomitants of depression in first episode schizophrenia, Phahladira et al. (2021) found a 5% prescription rate of antidepressant medications. Therefore, DS are probably under-recognized and under-treated in FEP patients- additionally due to the emphasis - on treating negative and positive symptoms (Upthegrove et al., 2014; Griffiths et al., 2021).

Psychopathological considerations

The findings of this research showed that the most relevant association of DS in FEP was with *positive symptom* severity levels, both at entry and as longitudinal changes in subscores over the – two years of follow-up. In accordance with Phahladira et al. (2021), the relationship between depressive and positive domains in early psychosis could be particularly important at a "symptom-level", reflecting state-related fluctuations in positive symptoms. This consideration is also partly concordant with the intrinsic hypothesis of depression in psychosis, - suggesting that DS could - follow the development of positive symptoms (Herniman et al., 2019).

DS in our FEP population were also associated with *negative symptom* severity levels, both at entry and as longitudinal changes in subscores – during the follow-up. As negative and depressive characteristics are often hard to differentiate from one another in FEP, we can't ascribe causality to these simple quantitative relationships, which could be partly attributable to their phenomenological overlap (Chiappelli et al., 2014) and/

Table 2. *PANSS "Affect" factor scores and their longitudinal associations with sociodemographic data, 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)*

T0-T1 Delta "Affect" factor scores	B	SE	95% CI for B Lower	Upper	β	p	R^2 = 0.389 $F_{[df=17]}$ = 6.728 **p = 0.001**
Constant	-0.131	1.921	-3.923	3.660	-	0.946	
Gender (females)	0.946	0.589	-0.217	2.109	0.102	0.110	
Age at entry (in years)	-0.021	0.037	-0.094	0.052	-0.035	0.573	
Education (in years)	0.003	0.004	-0.004	0.011	0.049	0.414	
Ethnic group (non-white Caucasians)	1.398	0.766	-0.114	2.909	0.111	0.070	
DUP (in months)	-0.038	0.036	-0.109	0.034	-0.062	0.299	
T0 equivalent dose of Chlorpromazine (mg/day)	-0.069	0.100	-0.267	0.129	-0.044	0.493	
T1 equivalent dose of Chlorpromazine (mg/day)	0.011	0.010	-0.008	0.030	0.070	0.251	
T0 equivalent dose of Fluoxetine (mg/day)	0.005	0.010	-0.014	0.025	0.038	0.581	
T1 equivalent dose of Fluoxetine (mg/day)	0.018	0.008	0.002	0.034	0.149	**0.029**	
T1 number of individual psychotherapy sessions	-0.025	0.038	-0.101	0.050	-0.044	0.510	
T1 number of psychoeducational sessions for family members	0.071	0.057	-0.042	0.184	0.088	0.216	
T1 number of case management sessions	-0.021	0.015	-0.051	0.009	-0.088	0.164	
T0-T1 Delta "Positive Symptoms" factor score	0.306	0.060	0.189	0.424	0.413	**0.001**	
T0-T1 Delta "Negative Symptoms" factor score	0.103	0.042	0.020	0.186	0.190	**0.015**	
T0-T1 Delta "Disorganization" factor score	0.116	0.057	0.004	0.228	0.166	0.063	
T0-T1 Delta "Excitement/Resistance" factor score	-0.073	0.080	-0.231	0.086	-0.062	0.367	
T0-T1 Delta GAF score	0.007	0.025	-0.043	0.057	0.021	0.785	
T0-T2 Delta "Affect" factor score	B	SE	95% CI for B Lower	Upper	β	p	R^2 = 0.342 $F_{[df=17]}$ = 4.381 **p = 0.001**
Constant	1.963	2.806	-3.583	7.509	-	0.485	
Gender (females)	0.674	0.821	-0.948	2.296	0.060	0.413	
Age at entry (in years)	-0.035	0.054	-0.142	0.073	-0.046	0.524	
Education (in years)	-0.005	0.005	-0.015	0.005	-0.073	0.302	
Ethnic group (non-white Caucasians)	0.604	1.015	-1.403	2.610	0.042	0.553	
DUP (in months)	0.018	0.054	-0.089	0.124	0.024	0.740	
T0 equivalent dose of Chlorpromazine (mg/day)	-0.126	0.142	-0.406	0.155	-0.068	0.377	
T2 equivalent dose of Chlorpromazine (mg/day)	-0.105	0.047	-0.197	-0.012	-0.160	**0.027**	
T0 equivalent dose of Fluoxetine (mg/day)	0.045	0.016	0.014	0.076	0.239	**0.006**	
T2 equivalent dose of Fluoxetine (mg/day)	0.014	0.011	-0.007	0.035	0.092	0.203	
T2 number of individual psychotherapy sessions	0.068	0.033	-0.003	0.133	0.160	**0.039**	
T2 number of psychoeducational sessions for family members	0.069	0.056	-0.041	0.180	0.101	0.216	
T2 number of case management sessions	-0.001	0.012	-0.025	0.023	-0.006	0.940	
T0-T2 Delta "Positive Symptoms" factor score	0.242	0.086	0.072	0.413	0.250	**0.005**	
T0-T2 Delta "Negative Symptoms" factor score	0.158	0.066	0.027	0.288	0.212	**0.018**	
T0-T2 Delta "Disorganization" factor score	0.091	0.080	-0.068	0.250	0.125	0.260	
T0-T2 Delta "Excitement/Resistance" factor score	-0.148	0.108	-0.361	0.065	-0.116	0.171	
T0-T2 Delta GAF score	-0.027	0.033	-0.092	0.038	-0.062	0.416	

Legend. PANSS = Positive And Negative Syndrome Scale; Pr-EP = Parma-Early Psychosis Program; FEP = First Episode Psychosis; T0 = Baseline assessment; 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.

or to secondary negative symptoms as consequences of clinically relevant depressed mood (Pelizza et al., 2022c; Pelizza et al., 2022d).

Additionally, given the longitudinal stability of DS associations with negative and positive dimensions, depressive features in FEP could also be considered as a longitudinally *stable index of psychopathological severity* over time. - Regarding this, Birchwood et al. (2005) postulated that DS could develop in early psychosis mainly due to the intrinsic disease process and/or negative cognitive appraisals of the meaning and experience of psychotic symptoms. The disruption and unfavorable impact that FEP can have on their interpersonal relationships, their vocational/educational goals and their identity construction, is particularly crucial during the critical developmental phase of young adulthood and/or adolescence (Poletti et al., 2019).

The results of this investigation also supported a significant association between *functioning deterioration* and DS at baseline. Previous findings on this topic were mixed, with some studies reporting poor daily functioning in FEP subjects with clinically relevant DS (Minor et al., 2015), and others showing no relationship (Cotton et al., 2012; Pelizza et al., 2020d). Such inconsistent results could be due to third variables that can mediate the association (e.g., personality features, neurocognitive factors).

Treatment considerations

The findings of this investigation showed a *reduction in DS* during the 24-month follow-up period.

This supports the results by Phahladira et al. (2021), who found that depressive psychopathology in first episode schizophrenia was greatest at entry, with the most significant decrease during the first 3 months of intervention and improvement maintenance along 2 years of follow-up. In this investigation, this reduction was positively associated with both the number of individual psychotherapy meetings supplied across the first 12 months of the Pr-EP intervention and the equivalent dose of antidepressant drug prescribed at baseline and during the first year of treatment. Moreover, it was negatively associated with the equivalent dose of antipsychotic medication prescribed at the end (T2) of our study.

Empirical evidence on treatment response for DS in FEP is overall quite poor. - Regarding this, even if *individual psychotherapy* (especially Cognitive-Behavioral Therapy [CBT]) showed indirect beneficial effects on depressed mood and suicidal behavior in early psychosis (Morrison et al., 2020; Pelizza et al., 2020e), no CBT investigation has - yet specifically explored depressive features in FEP (Upthegrove et al., 2017). Therefore, randomized clinical trials to replicate effectiveness of individual psychotherapy on DS in FEP are needed.

Furthermore, our evidence on a significant negative relationship between longitudinal reduction in DS levels and *antipsychotic* dosage at the end of follow-up could suggest a potential, direct "depressogenic effect" of antipsychotics in FEP patients (Phahladira et al., 2021). In this respect, a potential lack of improvement in positive symptoms over time - may lead to an increase in the prescribed dose of antipsychotics, resulting in a vicious - cycle worsening comorbid depressive psychopathology in FEP (Pelizza et al., 2022e).

Finally, the 1-year longitudinal prescription of *antidepressant* drugs was associated with improvements in DS levels at the end of our follow-up. This is not in line with what was reported in the current literature (Gregory et al., 2017; Dai et al., 2018), overall suggesting no association between severity in clinical depression and prescription of antidepressants in early psychosis. Further studies in larger FEP populations to support our promising results are thus needed.

Limitations

A first limitation of this investigation is related to the sample characteristics. Indeed, we explored FEP subjects in a "real-world" therapeutic setting, primarily aimed at delivering EIP interventions within community mental healthcare centers. Thus, our findings can be exclusively compared to analogous clinical groups. In addition, even if one of the - strengths of this investigation was the enrollment of patients at the psychosis onset, our evidence cannot be generalized to people at different phases of the disease (such as those with prolonged psychosis).

Moreover, the current investigation was designed within an EIP program not specifically focused on DS in FEP. Psychopathology was evaluated with the PANSS, an instrument widely administered in FEP samples, but poorly articulated for measuring DS. Future studies exploring DS with more specific tools for depression in psychosis (e.g. the Calgary Depression Scale for Schizophrenia [CDSS]) (Addington et al., 1990) are needed.

Third, we used a 5-factor structure of the PANSS (Shafer & Dazzi, 2019) and derived the affect dimension score from this structure, which has not yet reached a broad consensus. Thus, this limitation needs to be further explored before directly comparing our results with other instruments more specific - to measuring DS in psychosis. - Thus, given the common administration of the PANSS in FEP populations, our investigation has the potential to be replicated in analogous samples. This is of primary clinical relevance, since studies examining therapeutic effects of EIP treatments on DS at the psychosis onset - are still - limited and DS are associated with negative long-term outcomes.

Another weakness is intrinsically associated with the PANSS "Affect" domain subscore. Indeed, although it includes specific depressive features (such as PANSS "Depression" and "Guilt feelings" items), other items are not specific enough for depression, but describe psychopathological characteristics more related to the anxiety domain. Thus, future investigations using more appropriate – instruments for the investigation of DS in FEP, are needed.

Finally, our treatment parameters (e.g., the number of individual psychotherapy) were not randomly attributed. This restricts our ability to derive causal conclusions on the reported longitudinal associations with changes in DS severity levels. Indeed, these correlations could also depend on other plausible explanations (e.g., FEP subjects with more severe psychopathology could get more intensive interventions and improve the most, – in part because they - required the most treatment).

Conclusions

DS are relevant in FEP and could be considered not exclusively as a superimposed comorbidity, but also as an inextricable clinical dimension of the disorder. An in-depth assessment of comorbid DS is therefore crucial at the first presentation of FEP subjects into EIP services, specifically to prevent suicide and to ameliorate long-term outcomes. The results of this investigation showed a longitudinal improvement in DS over time, which was significantly related to the intensity of individual psychotherapy meetings specifically targeting DS in people with early psychosis, together with antidepressant therapy.

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