Comprehensive Psychiatry 86 (2018) 60–66

Contents lists available at ScienceDirect

Comprehensive Psychiatry

journal homepage: www.elsevier.com/locate/comppsych

Consequences of persistent depression and apathy in first-episode psychosis — A one-year follow-up study

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ARTICLE INFO

Available online xxxx
Keywords:
First-episode psychosis
Depression
Negative symptoms
Apathy
Persisting
Outcome

ABSTRACT

Background: Apathy and depression are prevalent in first-episode psychosis (FEP), have overlapping clinical features and are linked to social dysfunction, with indications that persisting symptoms have an even more negative impact. Our objective was to investigate the prevalence of persisting depression (PD), persisting apathy (PA), to what extent they overlap and their relative associations to functioning during a one-year follow-up.
Methods: One hundred and twenty-five participants with a FEP were recruited, and 88 (70%) were reassessed at follow-up. Functional outcome was assessed with the Global Assessment of Functioning Scale-split version, functioning sub-scale, apathy with the Apathy Evaluation Scale, Clinician version (AES-C), and depression with the Calgary Depression Scale for Schizophrenia (CDSS). Persisting depression was defined as a CDSS sum-score > 7 at baseline and follow-up, and persisting apathy as an AES-C sum-score ≥ 27 at baseline and follow-up. Multiple linear regression analyses were used to investigate symptoms' contributions to functioning. Differences in functioning between groups were explored with Kruskal-Wallis test and Mann-Whitney *U* test.
Results: We found PD in 17 (19%) and PA in 28 (32%) of participants. The likelihood of PD was increased if PA was also present ($p = 0.008$, phi = 0.28). Ten participants (11%) experienced overlapping PD and PA. Participants with PD ($r = -0.38$, $p = 0.004$), PA ($r = -0.51$, $p < 0.000$) or both ($r = -0.52$, $p < 0.000$) had poorer functioning at follow-up than participants without persisting symptoms.
Conclusion: PD, PA and overlapping PD/PA is highly prevalent and associated with severely impaired functioning in FEP. Correct identification of these patients is a prerequisite for initiating relevant treatment early in the course of illness.

1. Introduction

Functional disabilities are pronounced in schizophrenia and related psychotic disorders [1], and are often present at the start of the first psychotic episode. Negative symptoms have long been recognized as a central phenomenon in these disorders [2,3], with significant influence on the risk of disabilities [4].

Previously, affective symptoms have been considered positive prognostic factors in psychotic disorders [5]. However many, but not all [6,7], recent studies link depression to reduced everyday functioning, quality of life and increased suicidality [8–11]. Depressive symptoms are highly prevalent both in the prodromal phase [8,12], during and between acute psychotic episodes in schizophrenia [13,14]. Being more common in early stages of illness, prevalence rates of depression range between 14 and 45% at baseline in first-episode psychosis (FEP) studies [5,15]. The wide variability may be explained by heterogeneity in study designs. Though depression is known to wax and wane throughout the course of the disorders [12,16], 14–26% of people with FEP are found to be continuously depressed in 12–18 months follow-up studies [6, 8, 17], i.e. having persisting depression (PD). Functional impairments are shown to be worse in people with PD than in people with fluctuating depression [6,8,18].

Clinical expressions of depression and negative symptoms can be phenomenologically similar [19,20], including loss of motivation and withdrawal from activities. However, differentiating depression from negative symptoms is essential in order to offer appropriate treatment [21,22]. During the last decade our understanding of the phenomena underlying negative symptoms has improved. Five different sub-symptoms can be grouped into two sub-domains: avolition/apathy (from here on called apathy), anhedonia and asociality, i.e. the "experiential domain", and blunted affect and alogia, i.e. "the expressive domain" [23]. Research on sub-symptoms is expected to give more

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https://doi.org/10.1016/j.comppsych.2018.07.015
0010-440X/

knowledge about etiology and outcome, and harbors the potential for developing new treatments of negative symptoms [24].

Apathy, the best studied sub-symptom, is defined as a lack of goal directed behavior due to reduced motivation [25]. Studies indicate that beyond other negative sub-symptoms, apathy has a pivotal role in predicting poor functioning across psychotic disorders [2,26–28]. FEP-studies imply that apathy is prevalent early in the course of illness, with clinically significant levels (two standard deviations above mean in healthy controls) occurring in 50% at baseline assessments [29]. Between 16 and 30% have persisting apathy (PA) at short or long term follow-up [28,30,31]. Moreover, like for PD, PA has a stronger negative impact on functioning than fluctuating apathy [30,32,33].

In sum, persisting depressive and apathetic symptoms are of great concern as they seem to predict future functional impairment more strongly than fluctuating symptoms. Concurrently evaluating apathy and depression is necessary to assess their relative contributions to functional outcome. The prevalence of PD and PA in FEP and to what extent they overlap is not known, nor are their associations with functional outcome.

This study is a one-year follow-up of people with FEP. The aims are to explore:

1) the associations of current levels of depression and apathy with functioning at baseline and follow-up.
2) the prevalence of PD and PA and to what extent they overlap over the follow-up.
3) the relative contributions of PD and PA to functioning at follow-up.

As the associations between depression and functional impairment seem less unambiguous than for apathy, we hypothesized 1) that levels of apathy would be more consistently associated with reduced functioning in the cross-sectional analyses than depression 2) a more profound impact on functioning by PA than PD and 3) that PD and PA have additive negative effects on functioning at follow-up.

2. Materials and methods

2.1. Participants

Participants were consecutively recruited to the Thematically Organized Psychosis (TOP) study from four psychiatric units (inpatient and outpatient) in Oslo, Norway. We included 125 participants within a broad psychosis spectrum; schizophrenia, schizoaffective and schizophreniform disorders, bipolar I and major depressive disorders with psychotic symptoms, delusional disorder, brief psychotic disorder and psychosis not otherwise specified. This approach was chosen based on reports showing similar likelihoods of negative symptoms in schizophrenia spectrum and affective psychoses, and to avoid excluding participants based on diagnoses known to be unstable early in course of illness [31,34]. Participants were not considered FEP if they had previously been adequately treated for psychosis, defined as hospitalization or antipsychotic medication in adequate dosage for ≥ 12 consecutive weeks (or until remission within these 12 weeks). Participants were eligible for inclusion within 52 weeks following the start of first adequate treatment.

The Regional Committee of Research Ethics and the Norwegian Data Inspectorate approved the study. All participants gave an informed, written consent. At one-year follow-up, 88 (70%) participated.

Exclusion criteria were: Previous moderate/severe head injury, present medical or neurological condition with relationship to psychosis, not speaking a Scandinavian language, age outside the range of 18–65 years, IQ < 70 and psychosis due to substance use.

2.2. Instruments and measures

An extensive clinical assessment was performed by trained medical doctors or psychologists at baseline (BL) and follow-up (FU). Participants were diagnosed using the Structured Clinical Interview for the DSM IV (SCID-1) [35]. Interrater reliability of diagnostic categories was satisfactory, with an overall kappa of 0.77 [36]. Symptom levels were measured with the Positive and Negative Syndrome Scale (PANSS). We report on the Wallwork five factor model consisting of 20 items divided into positive, negative, disorganized, depressed and excited factors [37].

Functioning was measured with the Global Assessment of Functioning Scale-Split version [38], functioning sub-scale (GAF–F). Premorbid functioning was assessed with Premorbid Adjustment Scale (PAS) [39]. Scores from each interval (childhood: <11 years; early adolescence: 12–15 years; late adolescence: 16–18 years) were split into social and academic domains. As PAS-scores were highly correlated between age-intervals and the adolescence scores could be confounded by psychosis onset, we only used childhood scores in our analyses. Duration of Untreated Psychosis (DUP) was defined as the number of weeks from the first psychotic symptom (scored ≥4 on PANSS-items p1, p3, p5, p6 or g9) until first adequate treatment [40].

Apathy was assessed with the Apathy Evaluation Scale-Clinician version (AES-C) [41]. AES-C starts with an interview about hobbies, activities and descriptions of a "typical day" during the last month. Then, items like "She gets things done during the day" and "She is interested in learning new things" are scored from 0 through 4 on a Likert scale. Originally, AES-C has 18 items. We used an abridged 12-item version shown to have better psychometric properties in FEP. A sum-score ≥ 27 was set as cut-off for clinically significant apathy (2 standard deviations above mean in healthy controls) [42].

Depressive symptoms were measured with the Calgary Depression Scale for Schizophrenia (CDSS) [43]. CDSS outperforms other scales in differentiating between depression, extrapyramidal side-effects and negative symptoms in schizophrenia [21]. A major depressive episode is predicted with 91% specificity and 85% sensitivity at a cut-off of >7 [44]. To ensure a high specificity, we chose >7 as the cut-off for a clinically significant depression. Alcohol use was measured with Alcohol Use Disorder Identification Test (AUDIT) [45], and drug use with Drug Use Disorder Identification Test (DUDIT) [46].

2.3. Persisting symptoms groups

We divided the FU sample ($n = 88$) into groups based on the following criteria: 1) participants with a CDSS-score > 7 at both BL and FU were defined as having PD, 2) participants with an AES-C-score ≥27 at both BL and FU were defined as having PA, and 3) participants with depression or apathy above cut-off at only one assessment were defined as having non-persisting symptoms, together with the group with scores below cut-off at both BL and FU. We then defined four mutually exclusive groups:

$$\text{nAnD} = \text{non}-\text{persisting apathy} + \text{non}-\text{persisting depression}$$

$$\text{PDnA} = \text{persisting depression} + \text{non}-\text{persisting apathy}$$

$$\text{PAnD} = \text{persisting apathy} + \text{non}-\text{persisting depression}$$

$$\text{PAPD} = \text{persisting apathy} + \text{persisting depression}$$

2.4. Statistics

Analyses were carried out using the IBM Statistical Package for the Social Sciences (SPSS Inc.), Version 23. Violations of assumptions of normality, homoscedasticity, linearity and multicollinearity were