Emerging symptoms on the pathway to psychosis
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Chapter 8

Longitudinal course of negative and depressive symptoms and the association with functional outcome in patients with an at risk mental state for psychosis

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submitted
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Visual impression of chapter 8
Abstract:

Background: Subjects with an at risk mental state (ARMS) for developing psychosis show a variable functional outcome, with or without transition to psychosis. Little is known about the course of depressive and negative symptoms in ARMS subjects, and their association with functional outcome over time.

Method: 18-months follow-up data of 201 help-seeking ARMS subjects were evaluated. The course of depressive and negative symptoms was analyzed with mixed model linear regression analyses, their association with functional outcome was evaluated using standard linear regression analyses.

Results: Both depressive and negative symptoms were found to decline significantly over time, with the largest reduction occurring within the first 6 months after baseline. Changes in depressive symptoms are only weakly associated to changes in negative symptoms. At baseline, lower levels of both depressive and negative symptoms were associated with a better functional outcome after 18 months. Moreover, a decline in the first 6 months of both depressive and negative symptoms was associated with better functional outcome after 18 months.

Conclusions: The association between negative and depressive symptoms and functional outcome suggests that negative and depressive symptoms deserve attention as potential targets for early detection and treatment, not only to reduce the risk of transition, but also to improve functional outcome.
Introduction

The success of early detection and intervention in first episode psychosis has led to an increased interest in the period prior to a first episode of psychosis. Commonly, the pre-psychotic phase is denoted as either the ultrahigh risk (UHR) phase, or the at-risk mental state (ARMS) phase. The UHR/ARMS criteria can be classified into three categories: attenuated positive symptoms, brief limited intermittent psychotic symptoms and having a genetic risk combined with reduced social functioning. These criteria have been tested over the last 15 years and were found to predict the onset of a first episode of psychosis at rates several hundred-fold above the incidence of psychosis in the general population. Traditionally, ARMS research mainly focuses on the presence of attenuated positive symptoms. However, other psychiatric symptoms may also be important predictors of transition to florid psychosis.

Negative symptoms are highly prevalent in ARMS subjects (up to 40%). In addition, recent studies also underlined the predictive value of negative symptoms for developing a psychosis. Furthermore, depressive symptoms, highly prevalent in ARMS (30-40%), have also been found to predict psychosis. Depressive and negative symptoms show a considerable clinical overlap. Nonetheless, an investigation of the course of depression and negative symptoms longitudinally in an ARMS sample may reveal some of their differences. Depressive symptoms may be more reactive to stress and life events, resulting in fluctuations over time, whereas premorbid (primary) negative symptoms may reflect the underlying neurodevelopmental disorder and may consequently be more stable.

Merely focusing on the emergence of florid positive symptoms of psychosis (i.e. hallucinations and delusions) as defining outcome variable for transition may be a too limited approach. After all, a large body of research shows that in psychotic disorders, prominent negative symptoms are associated with low functional outcome and considerable impairments in social functioning. Therefore, investigating depressive and negative symptoms and their association with social functioning might lead to a better insight into the core features of ARMS.

Based on these considerations we investigated two research questions:

1) the course of negative and depressive symptoms in an ARMS sample including their longitudinal relationship and;

2) the relationship of negative and depressive symptoms with functional outcome.
We tested the following hypotheses:

1) depressive symptoms in ARMS subjects become less severe over time, whereas negative symptoms are more persistent;
2) the severity of both depressive and negative symptoms is associated with poor functional outcome.

**Material and Methods**

**Sample and procedure**

This study analyzed data from the Early Detection and Intervention Evaluation (EDIE-NL) study. This was a randomized clinical trial in ARMS patients comparing treatment as usual (TAU) with an add-on cognitive behavioral therapy (CBT-ARMS) in order to prevent transition to psychosis. The EDIE-NL study has been approved by the Dutch Union of Medical-Ethics Trial Committees for mental health organizations. The trial was conducted in compliance with the 'Declaration of Helsinki' (amendment of Edinburgh, 2000). The trial is registered with Current Controlled trials as trial number ISRCTN21353122. Details of the study have been published elsewhere. Informed consent was obtained in writing from all participants. In addition, the parents gave informed consent for subjects under 18 years of age.

As part of the EDIE-NL study, help-seeking subjects (aged 14-35) who entered mental healthcare at four sites in the Netherlands (Mental Health Centre PsyQ, the Hague; Academic Medical Centre and Mental Health Centre PsyQ, Amsterdam; Mental Health Centre Rivierduinen, Leiden; and Friesland Mental Health Care Services) were screened for the presence of attenuated psychotic symptoms with the Prodromal Questionnaire (PQ). One centre (AMC, Amsterdam) included patients who were referred on the basis of clinical ARMS indication. If people scored positively for 18 of 45 subclinical positive psychotic symptoms of the PQ, or after referral on suspicion of ARMS, they were interviewed with the Comprehensive Assessment of At Risk Mental States (CAARMS). Patients were eligible for inclusion if they met the following criteria: (1) age 14-35 years; (2) a genetic risk or CAARMS scores in the range of the ARMS; and (3) an impairment in social functioning (a score on the Social and Occupational Functional Assessment Scale [SOFAS] of 50 or less, and/or a reduction by 30% on the SOFAS for at least 1 month in the past year. Subjects were excluded if they met any of the following criteria:
current or previous use of antipsychotic medication of ≥ 15 mg cumulative haloperidol equivalents; b) severe learning impairment; c) problems due to an organic condition; d) insufficient command of the Dutch language; e) a previous episode of psychosis.

The subjects were treated for the disorder for which they were seeking help. After adequately describing the study to the subjects, written informed consent was obtained. The study period lasted 18 months.

**Assessments**

The first screening for most centres was done with the *Prodromal Questionnaire (PQ).* The PQ is a 92-item self-report questionnaire that assesses the presence of lifetime prodromal symptoms on a two-point scale (true/false). Following the results of a pilot study, a cut-off score of ≥ 18 was used to refer subjects for a diagnostic interview using the CAARMS.

*Comprehensive Assessment of At Risk Mental State (CAARMS).* The CAARMS was used to assess the ARMS criteria, and to assess negative symptoms. The CAARMS is a semi-structured interview that assesses ARMS symptoms. The CAARMS consists of seven subscales that include: Positive Symptoms (4 items: unusual thought content, non-bizarre ideas, perceptual abnormalities, and disorganised speech), Cognitive (2 items), Emotional Disturbances (3-items), Negative Symptoms (3 items: alogia, avolition/apathy, anhedonia), Behavioural Change (4 items), Motor/Physical Changes (4 items) items and General Psychopathology (8 items). Intensity and frequency of the symptoms is scored on a 7-point Likert-scale and distress caused by the symptom on a 0-100 scale. The EDIE-NL investigators received training by A. Yung, one of the developers of the CAARMS criteria. Reliability checks of the Dutch version of the CAARMS were performed every three months during the study. The preliminary pairwise inter-rater concordance of the intensity subscales of the CAARMS was 0.81, which was considered acceptable. The negative symptoms score on the CAARMS (CAARMS-NEG) that is used in this paper, is the mean intensity score of the three negative symptoms items. The *Social and Occupational Functioning Assessment Scale (SOFAS)* was used to assess the level and possible decline of social and occupational functioning in the previous year. Furthermore, the scale was used for including patients in the study as well as at the assessment-moments. The SOFAS, ranging from 0 to 100, is a modified version of the Global Assessment of Functioning (GAF) scale, separating the assessment of social
and occupational functioning from the assessment of symptoms and psychological functioning.

The Beck Depression Inventory-II (BDI-II) and Calgary Depression Scale (CDS) Depression was assessed at all measurements with the BDI-II. Scores on the BDI-II range from 0-63 (0-13 = minimal depression; 14-19 = mild depression; 20-28 = moderate depression; 29-63 = severe depression). Clinical depression is defined as BDI score > 19. Depression was also assessed with the CDS, a 9-item interview that claims to assess depressive symptoms separately from the negative symptoms in patients with schizophrenia.

At baseline and at 6, 12, and 18 months (T0, T6, T12 and T12 respectively) the CAARMS and the SOFAS as well as the BDI-II were assessed. At baseline and T18 depression was also assessed with the CDS. All assessments were performed until patients experienced a transition to psychosis.

Statistical analysis

All analyses were performed with IBM SPSS Statistics, version 20.0. The relationship between BDI-II and CDS was quantified with the Pearson PM correlation coefficient.

Research question 1, the course of depressive and negative symptoms, including their longitudinal relationship, was assessed with mixed model regression analysis, with respectively BDI-II and the CAARMS-NEG as the dependent variable and time as the independent variable.

It is important to take into account that BDI-II and CAARMS-NEG were assessed at baseline, 6, 12, and 18 months only in patients who did not experience transition to psychosis. Of patients who made the transition to psychosis before the last measurement, only data until transition were available. For this reason, we employed pattern mixture modeling in order to be able to use all the available data until transition. The application of this method involves the division of the patients into three subgroups: group 1 with only baseline data (i.e. having a transition between baseline and 6 months; n=19), group 2 with a transition between 6 and 18 months (n=13) and group 3 with no transition up to 18 months (n=164).

The relationship between BDI-II and time was assessed by fitting the mixed model linear regression model $BDI-II_j = b_0 + b_1t_1 + b_2t_2 + b_3t_3$ ($j=0, 1, 2, 3$) to all 3 subgroups separately. In this model, time is considered a categorical variable operationalized in three dummy dichotomized (0,1) variables ($t_1$, $t_2$, $t_3$) with $t_j = 1$ if measurement occasion= $j$.
and 0 if measurement occasion is other than \( j \). Baseline, \( b_0 \) is the reference category (i.e., mean BDI-II score at baseline), the mutual dependence between the subsequent measurements is modelled by an unstructured covariance matrix. In this model, \( b_j \) is the difference in mean BDI-II score at measurement occasion \( j \) and the mean baseline BDI-II score.

In this regression model, the intercept \( (b_0) \) can be seen as the mean baseline score, \( b_1 \) as the change between baseline and 6 months and \( b_2 \) as the change between baseline and 12 months and \( b_3 \) as the change between baseline and 18 months. While the intercept \( (b_0) \) can be assessed in all three groups, the second regression coefficient \( (b_1) \) can only be obtained for groups 2, 3 and 4 and the third and fourth regression coefficients \( (b_2 \) and \( b_3 \)) only applied to group 4. The estimates from three regression analyses (one for each group) were combined into an overall regression analysis, thus using all the available information to assess the course of depressive and negative symptoms. For these latter analyses all patients (\( n=196 \)) were used.

The relationship between CAARMS-NEG and time was assessed in a comparable way. The subsequent analyses (longitudinal relationship between BDI-II and the CAARMS-NEG and the relation between BDI and CAARMS-NEG with social functioning at 18 months (SOFAS-T18) data from the non-transition group only (\( n=164 \)) were used. This was done because data pertaining to the changes over time for both BDI and CAARMS-NEG were only available for this group and furthermore, in this approach the relation between depression symptoms and negative symptoms at baseline with SOFAS-T18 would not be confounded by transition to psychosis.

The longitudinal relationship between BDI-II and CAARMS-NEG was studied with the following mixed model regression model \(^{44}\),

\[
CAARMS-NEG_{t=j} = b_0 + b_1 BDI_{t=0} + b_2 (BDI_{t=j} - BDI_{t=0}), \quad j = 0, 1, 2, 3
\]

which allowed us to distinguish the longitudinal (within-person) from the cross-sectional (between-person) effect of the BDI-II on CAARMS-NEG score.

In this model, \( b_2 \) can be interpreted as the longitudinal (within-person) effect, i.e., the association between changes in BDI over time and changes in CAARMS-NEG over time. \( b_1 \) can be interpreted as the cross-sectional (between-person) association between (baseline) BDI scores and (baseline) CAARMS-NEG scores.

Research question 2, the relationship between depression and negative symptoms and functional outcome was assessed with 4 linear regression analyses; the first two with social functioning at T18 as dependent variable and baseline social functioning as covariate and respectively BDI or CAARMS baseline as predictor; the second two were
similar except the predictor being the change between BDI-II at baseline and 6 months or the change between CAARMS-NEG at baseline and 6 month as predictor.

The differences in magnitude between the regression parameters of BDI and SOFAS are difficult to interpret because both scales have different ranges. For this reason we used Akaike's Information Criterion (AIC) to compare the effect of two scales (BDI and SOFAS) on social functioning. The model with the lowest AIC is the best model given the data.

Results

Demographic characteristics

5,705 patients were screened with the PQ between February 2008 and February 2010. Of these, 864 patients had a score ≥ 18 on PQ; these patients were interviewed with CAARMS, as well as the patients referred to AMC Amsterdam. The CAARMS results showed that 104 of the preselected patients met the psychosis criteria, even though their condition was not recognised during intake at the mental health institutions or by general practitioners at referral. These patients were excluded from the study. Of the remaining 760 patients, 302 patients met the ARMS criteria. Of these 201 patients gave informed consent and were randomized to CBT-ARMS plus TAU (n=98) or TAU (n=103). After randomization, 2 patients turned out to have met psychosis criteria before randomization and 3 patients reported they had been treated with antipsychotic medications for a psychotic disorder in the past. These 5 patients fulfilled the exclusion criteria in retrospect and were removed from the study. All analyses pertain to the remaining 196 patients.

Baseline characteristics of the 196 ARMS patients comprising the study sample are presented in table 1.

Of the 196 patients at baseline, 194 completed the BDI, 190 the CDS and 189 both. There was a strong, positive correlation between BDI and CDS total scores at baseline (r=.693, p<0.001, n=189). At T18, 136 patients completed the BDI, 161 the CDS, and 134 both. Also at T18 we found a strong, positive correlation between the BDI and CDS (r=.788, p<0.001, n=134).
The course of depressive and negative symptoms

Both depressive (Table 2) and CAARMS negative symptoms (Table 3) declined significantly over time, with the largest decrease within the first 6 months after baseline (figure 1). The steeper fall in the depressive symptoms relative to the negative symptoms is due to the fact that the BDI has a larger scoring range than the CAARMS-NEG.

In terms of Cohen’s d (which is insensitive to scale) the BDI decline within the first 6 months is in fact smaller than the CAARMS-NEG decrease (BDI, d=.47; CAARMS-

Figure 1 18 months course of depressive symptoms (assessed with the BDI-II) and negative symptoms (assessed with the CAARMS negative symptom scale).

BDI=total score BDI, CAARMS-NEG=total intensity score of the negative symptom items of the CAARMS

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NEG, d=.60). After 12 months the decline is almost negligible for both the BDI and the CAARMS (Cohen’s d for BDI is .13 and for the CAARMS .10).

The number of patients fulfilling criteria for clinical depression (BDI>19) was 57.1% at baseline, 34.2% at 6-months, 27.8% at 12 months, and 22.6 % at 18 months. The number of patients with a SOFAS score of 60 or higher (reasonable level of functioning) was 0% at baseline, 35.2 % at 6-months, 47.3 % at 12 months, and 54.2 % at 18 months.

The changes in depressive symptoms over time are statistically related to the changes in negative symptoms (table 4). The regression analysis distinguished between a cross-sectional (between-person) relation and a longitudinal (within-person) relation. Both are statistically significant p<0.001. Given the regression model, a decrease of 1 BDI point predicts a decrease in 0.21 CAARMS-NEG point.

The explained variance of the model, however, is relatively low, suggesting that changes in BDI are only weakly related to changes in CAARMS-NEG. The correlation between the change in depressive symptoms and the change in negative symptoms between T0 and T6 was 0.352 (p<0.001) and the correlation between baseline and T18 was 0.307.
Relation between (the course of) depressive and negative symptoms and social functional outcome

Controlling for baseline social functioning, both the level of baseline depressive symptoms and negative symptoms were negatively related to functional outcome at 18-month follow-up (BDI-II; $b=-0.41$, se($b$)=.099, $t(130) = -4.14$, $p < .001$, Akaike Information Criterion AIC=1046.8 and CAARMS-NEG, $b=-0.92$, se($b$)=0.33, $t(130)$ =-2.78 $p=.006$ AIC= 1053.1).

This means that a person with 1 point higher score on baseline depression has 0.41 point lower social functioning at 18 month follow-up. A person with 1 point higher baseline negative symptoms has a 0.92 point lower social functioning at 18-month follow-up. Given the fact that the BDI has a larger scoring range than the CAARMS-NEG, this does not imply that the association is stronger for negative symptoms than for depression. In fact the correlation between baseline depression and social functioning at 18-month follow-up ($r=-.37$) is stronger than baseline negative symptoms and social functioning at 18-month follow-up ($r=-.27$).

As the depressive and the negative symptoms showed the strongest decrease in the first 6 months, we furthermore assessed the relation between their changes in that period with social functioning at 18-month follow-up, controlling for baseline social functioning. Both were found to be negatively associated with social functioning. A decline in depression or negative symptoms between baseline and 6-month follow-up is related to a higher social functioning at 18-month follow-up (BDI-II T0-T6; $b=-.38$, se($b$)=.134, $t(111)=-2.86$, $p = .005$ AIC = 902.6; CAARMS-NEG T0-T6; $b=-.75$, se($b$)=.325, $t(111)=-2.31$, $p = .023$, AIC= 903.2). The comparable AIC's suggest that BDI-II change...
and CAARMS-NEG change explain social functioning equally well. The Pearson pm correlations with social functioning at 18-month follow-up are somewhat stronger for depression (BDI-II T0-T6: \( r=-.24, p=.009 \)) than for negative symptoms (CAARMS-NEG T0-T6 scores: \( r=-.20 \) (\( p=.029 \)). The explained variance is very modest: change in depressive symptoms and change in negative symptoms during first 6 months after baseline each explain approximately 5% of the variance in social functioning at 18 months follow-up.

**Discussion**

In this study we found that that both depressive and negative symptoms in ARMS subjects decrease over time. Against our expectations, both the severity of depressive and negative symptoms decreased in a similar way. Although we found the expected overlap in depressive and negative symptoms, only a small proportion of the change in the depressive symptoms is associated with the change in the negative symptoms and vice versa. This suggests that the depressive and the negative symptoms reflect independent symptom clusters.

Both the negative- and the depressive symptoms at baseline were negatively associated with social functioning at 18 months follow-up. However, the association was slightly stronger for the depressive symptoms. Moreover, a decrease in both the depressive and the negative symptoms in the first six months, was positively associated with better social functioning at 18-month follow-up.

Our results with respect to the course of negative symptoms are similar to those reported by Addington and colleagues \(^{47}\) who found a significant improvement of negative symptoms in ARMS subjects in the first year. Piskulic and colleagues \(^{16}\) found negative symptoms to be more persistent, and in case of high severity and persistence to be associated with transition to psychosis. We extended the findings by looking at the association with social functioning at 18 months, and by investigating depressive symptoms as well.

We expected that negative symptoms would be relatively stable, in contrast to depressive symptoms. However, we found that negative symptoms decreased as well. This finding is in contrast with the large body of literature on the phenomenology of negative symptoms in patients with full-blown psychotic disorder; in these patients negative symptoms are generally described as stable, prognostically unfavourable...
phenomena. Perhaps the assumption that negative symptoms are stable, enduring may only hold for those with long standing active psychosis, or those with a severe course of the disorder. In contrast, our sample consisted of young subjects exhibiting subclinical psychotic phenomena, of which the vast majority did not proceed to a fully psychotic state. Interestingly, in a recent study, 75% of first episode psychotic patients showed a reduction in negative symptoms over 3 years, and Kirkpatrick and colleagues found enduring negative symptoms in only 15% of their first episode patient group. These findings suggest that negative symptoms might, in some patient populations, be less stable than previously thought. Another explanation might be that during the early, pre-psychotic phase some negative symptoms are reversible, whereas negative symptoms that continue to be present until a florid psychotic disorder has developed, may have become resistant to treatment. This may in fact underscore the importance of the early intervention concept.

The association found in our study between depressive and negative symptoms at baseline and social functioning after 18 months is in accordance with a large retrospective study about prodromal symptoms of schizophrenia, as well as with a recent prospective ARMS study. We extended these findings by showing that a decline in both the negative and depressive symptoms is independently associated with better social functioning over time. However, we should point out that the explained variance of change in SOFAS score in relation to depression as well as negative symptoms is only 5%. Our study also shows that the social outcome of the ARMS group is very heterogeneous. The proportion of respondents with a SOFAS score of 60 or more increased from 0% to 54% during 18 months follow-up. However, 46% still had a SOFAS score below 60 at 18 months.

To our best knowledge this is the first prospective study evaluating both depressive and negative symptoms in ARMS patients. Our study is also the first to focus on social functioning as primary outcome.

The strength of our study is that a relatively large number of ARMS subjects was included and followed. In addition, we include data of all the patients irrespective of whether or not there was transition to psychosis. Our findings are subject to some limitations. Firstly, our follow-up was limited to 18 months, hereafter, important changes in depressive- or negative symptom, or social functioning may occur. Secondly, patients who experienced a transition during the follow-up period were not followed up in the same way as those subjects who did not make a transition. As a result, some analyses could only be performed in the non-transition group. However, the use of
pattern mixture modelling maximized the range of data used, including initial data of those who did make a transition to psychosis.

In conclusion, we have shown that both depressive and negative symptoms improve during the course of the ARMS, and that both negative and depressive symptoms at baseline are negatively associated with functional outcome. Importantly, negative symptoms improved also, showing that this symptom cluster, which is clinically notorious for treatment resistance in schizophrenia patients, may still be open to modification in ARMS subjects.

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