Emerging symptoms on the pathway to psychosis
Klaassen, Rianne

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Chapter 9

Summary, Conclusions and Discussion
Summary

The objective of this thesis was to increase our knowledge about emerging psychotic symptoms on the pathway to a first psychosis. To this end we investigated positive, negative and depressive symptom clusters and focused on the following aims:

Aim 1: acquiring a better understanding of emerging positive psychotic symptoms by asking whether positive psychotic symptoms can be detected early and if this is useful clinically.

Aim 2: acquiring better understanding of negative, depressive symptoms, on the pathway to first episode psychosis.

We tried to answer the following questions:
2a: What role do these two symptom clusters play on the pathway to a first episode psychosis?
2b: can we distinguish these two symptom clusters from each other?

Aim 1: acquiring a better understanding of emerging positive symptoms on the pathway to first episode psychosis.

Question: can positive psychotic symptoms be detected early and is this useful?

Chapter 2 presents an overview of the High and Ultra-High Risk factors associated with a transition to a first psychotic episode and discusses the usefulness of screening patients with genetic dispositions as well as patients referred to mental health.

A screening of the general population is not considered to be of particular value due to the low rate of incidence of schizophrenia. In The Netherlands it is 0.025% or 4000 first psychosis cases annually. We concluded that few benefits accrue from the screening of people with a first-degree relative suffering from the disorder. While research has shown that the risk of a psychosis in this group is tenfold higher than that in the general population, the multiplicity of risk factors contributing to the development of schizophrenia means that 90% of this at-risk group does not develop a psychosis. However, early detection within the patient group referred to the Mental Health Care
appears to be useful. This approach needs further investigation if an evaluation of the efficacy of preventative treatment prior to the development of the first psychotic episode is to become a practical option.

It is known that many patients at risk of developing a psychotic disorder or experiencing a psychosis have been help-seeking for non-psychotic disorders prior to the onset of psychosis. Thus screening those patients entering the secondary mental healthcare services may offer practical help. In chapter 3 we explored the effectiveness of the two recruitment strategies used in the Dutch "Early detection and Intervention Evaluation" Study (EDIE-NL). This is a two-stage screening method in a consecutively help-seeking population entering the secondary mental health services for non-psychotic disorders against a population that was referred to a Diagnostic centre of an early Psychosis Clinic due to a suspected development of a psychotic disorder. The screening detected a threefold higher incidence of At Risk Mental State (ARMS) (0.025) compared to the referral strategy (0.008). Screening also revealed patients who already showed frank psychosis, without being noticed at intake in the secondary mental health. These findings indeed confirm the idea that screening in a help-seeking population entering the secondary mental healthcare services for non-psychotic problems can detect a group of patients in a late prodromal stage. However, these results are tentative and need further replication.

The term At Risk Mental State refers to a risk of transition to a first psychosis within a year. A recent meta-analysis by Fusar-Poli et al. yielded the following transition rates, independent of the psychometric instruments used: 18% after 6 months of follow-up, 22% after 1 year, 29% after 2 years, and 36% after 3 years (1). Although ARMS is associated with a very high risk of developing psychosis within the first 3 years, the proportion of false positive warrants further attention. The majority of cases of ARMS are included on the basis of the presence of attenuated positive symptoms; however, it is unclear if all positive symptoms are indicative of a similar risk. In chapter 4 we explored the role of bizarre and non-bizarre ideations, perceptual abnormalities, and disorganization in relation to transition. The most important factor affecting the risk of transition appeared to be the distress cause by the symptoms. Bizarre ideations and persecutory ideations (non-bizarre ideations) were more strongly related to the transition compared to the more common adolescent phenomena: non-bizarre
ideas such as magical thinking, grandiosity, or those perceptual abnormalities not accompanied by distress.

**Aim 2: acquiring a better understanding of negative, depressive symptoms, on the pathway to first episode psychosis.**

a) What role do these two symptom clusters play on the pathway to a first episode psychosis?

b) Can we distinguish between these two symptom clusters?

In chapter 5 we explored both the prevalence and the association of depression with positive and negative symptoms in three groups: first episode psychosis patients, their siblings and healthy controls. Depression is a clinically relevant dimension in patients with schizophrenia, and is associated with both positive and negative symptoms. However, it is unknown whether this also applies to siblings. Depressive symptoms and their association with positive and negative symptoms were examined in 813 healthy siblings of patients with a non-affective psychotic disorder, 822 patients and 527 healthy controls. First, we found that patients reported more lifetime depressed mood and more depressive episodes than both siblings and controls. Siblings exhibited a greater chance of meeting the criteria for lifetime depressive episodes than the controls.

In all three groups the number and duration of depressive symptoms were associated with (sub)clinical negative symptoms. The number of depressive symptoms in patients and siblings was furthermore associated with (sub)clinical positive symptoms. Finally, lifetime depressed mood showed familial clustering, though this clustering was absent for lifetime depressive episodes.

Our results show that although positive symptoms, negative symptoms and depressive symptoms are separate dimensions, or symptom clusters, they are related both on a clinical and a subclinical level.

Conclusion: The findings above suggest that a genetic vulnerability for both depressive and psychotic symptomatology may exist on a clinical as well as a subclinical level.

In our systematic review and meta-analysis (chapter 6) we showed that Duration of Untreated Psychosis (DUP) is associated with negative symptoms in addition to positive
symptoms, up to 8 years of follow-up. A non-linear relationship was found between an improvement in negative symptoms and DUP whereby people with a DUP shorter than 9 months showed substantially greater negative symptom reduction than those with a DUP of greater than 9 months.

The latter finding is consistent with the hypothesis that in many cases psychosis is a clinical manifestation of a progressive pathological process. However, the causality of this association remains unclear.

In chapter 7 we explored the symptoms in an ARMS population by performing an exploratory factor analysis of the Scale of Prodromal Symptoms (SOPS) in the Dutch part of the European Prediction of Psychosis Study (EPOS). Our aim was to differentiate between negative and depressive symptoms. Four factors were extracted from the SOPS: negative symptoms, depression, disorganized and positive symptoms.


The latter subscales were validated by means of (partial) correlations, with the PANSS Negative symptom score and the BDI total score. It was shown in this way that, depression and negative symptoms can be clearly differentiated.

However, ‘avolition’ and ‘deterioration in role functioning’ have moderate loadings on both factors, arguing against a too strict depressive/negative dichotomy. The same confusion between between negative and depressive symptoms in psychosis/schizophrenia research has led researchers also to conclude there is some overlap.

ARMS patients are help-seeking, distressed, and, irrespective of transition to psychosis, prone to persistent social problems. Little is known about the course of depressive and negative symptoms in ARMS subjects, and their association with functional outcome over time.

Chapter 8 describes the results of an 18 months follow up from 201 help-seeking ARMS individuals of the EDIE-NL study. Our analyses showed that both depressive and negative symptoms declined significantly over time, with the largest decline within the first 6 months after baseline. Changes in depressive symptoms are only weakly related to changes in negative symptoms. Both the level of baseline depression symptoms and negative symptoms and a decline in the first 6 months of these symptoms were related to functional outcome at 18 months.
Conclusions:

I think that the results of the studies, presented in this thesis, performed in various samples, have provided new perspectives on the emerging symptoms on the pathway to psychosis. To conclude, I will summarize the main conclusions, finishing with a discussion, a short return from research back to clinical practice, and some recommendations for future research.

1) Early detection of psychotic symptoms in secondary mental health care appears to be useful. Screening reveals a three-fold incidence of At Risk Mental State (ARMS) (0.025) compared to referral strategy (0.008). (Chapter 2,3).

2) Specific positive psychotic symptoms (bizarre ideations and persecutory ideations, perceptual abnormalities accompanied by distress) show a larger risk of transition to psychosis than others (magical thinking, grandiosity, perceptual abnormalities not accompanied by distress). (Chapter 4).

3) A genetic vulnerability for both depressive and psychotic symptomatology may exist on a clinical as well as a subclinical level (Chapter 5).

4) A shorter DUP is not only associated with reduced positive symptoms, but also with less severe negative symptoms at short and long term follow up (up to 8 years), especially when DUP is less than 9 months. (Chapter 6).

5) In an ARMS population “social anhedonia and withdrawal”, “decreased expression of emotion” and “decreased expression of emotions and self” appear to be core negative symptoms, whereas ‘dysphoric mood’ and “impaired tolerance to normal stress” seem to be core depressive symptoms. Avolition may be both a negative as well as a depressive symptom. (Chapter 7).

6) In ARMS subjects, depressive as well as negative symptoms show a decline over time. They are both positively and independently associated with a functional outcome. (Chapter 8).
Discussion
Discussion

Visual impression of the discussion
Discussion

From research answers back to clinical practice:

Patient Guus

Had Guus been referred to our outpatient unit using the two-step screening method, he would possibly have scored enough on some items to warrant an interview with CAARMS. It cannot be ruled out that besides an anxiety diagnosis, he would have also been classified with an ARMS, and received cognitive behavioral therapy designed for these complaints (2). His parents would then have been given psycho-education about his experiences, even though he did not have a psychosis at the time and his risk of becoming psychotic would have diminished by 50%. But even had he made a transition to psychosis, the stress to Guus and his parents caused by the diagnosis would have been reduced as a direct result of their being informed of the situation. Perhaps, his prognosis would have been better as well. In addition, by being referred to first psychosis teams focused on adolescents experiencing a psychosis, he could have avoided confrontation with older people with severe psychiatric problems on an adult ward.

Patient Jan.

It is good clinical practice to combine a diagnostiek interview with diagnostiek instruments. The attempts described in this thesis at differentiating between negative and depressive symptoms have revealed some to be more specific for depression and others to negative symptoms. However, I am not convinced that the answers presented here changed Jan’s diagnosis.

Jan was definitely suffering from “social anhedonia and withdrawal”, and “decreased experience of emotions and self”, both negative symptoms (3). However, as he also scored on the depressive questionnaire, we can assume he suffered also from a depressive mood, one of the core symptoms of a depression. Anhedonia, however, the absence of the capacity to experience pleasure is also part of a depression. The depressed mood is considered to have an additional dimension: the suffering, being irritable and/or sad as well as other emotions. Unfortunately, symptom scores on a depressive questionnaire do not give the complete answer to the question asked.
We might consider an alternative longitudinal approach to Jan’s case by looking at the origin of his symptoms. However, both negative and depressive symptoms have been described as the earlier signs prior to a psychosis (4); assuming depressive symptoms are variable in contrast to negative symptoms being more stable over time, is too simplistic (chapter 8).

So while I believe that the studies described in this thesis are helpful in distinguishing depressive from negative symptoms, it would not have changed my advice to Jan to try an antidepressant.

**General discussion**

Early detection and intervention have brought about considerable research and clinical effort: early detection of psychosis was first undertaken in the 1980’s, and since mid 90’s ARMS research has been a focus, leading to a more upbeat, hopeful treatment approach of psychosis/schizophrenia.

We have shown that screening of ARMS in secondary mental health care is a sensible approach and leads to an earlier detection of more patients with an ultra high risk to develop a psychotic disorder (6), (7). However, as not all positive symptoms have the same predictive validity (8) and the method of screening could benefit from further modifications. Some early detected mild positive psychotic symptoms are not specifically associated with a risk to develop a psychotic disorder. This may lead to false positives, which is in the light of inducing anxiety and stigma a problem. Besides this it is important to recognize that irrespective of the transition to psychosis ARMS patients are help-seeking, distressed, and prone to persistent social problems (5), (9).

Secondly, in the ARMS phase both depressive and negative symptoms co-occur. Although they are partly separate domains, negative symptoms are associated with DUP (10). Both negative as well as depressive symptoms are associated with social functioning after 18 months. The combination of information on positive, negative and depressive symptoms provides a broader focus then merely considering positive symptoms on their own. Our results underline the suggestion made by (1) to modify current inclusion criteria so as to include negative symptoms and mood disturbances.
One of our goals was to distinguish between negative and depressive symptoms. We have tried to do so in an ARMS sample by performing a factor analysis. This only yielded a partial sub-classification (see below).

**Depressive symptoms:** Depressed mood, disturbance in sleep and appetite impaired tolerance to normal stress, Guilt, Hopelessness, Suicidal thoughts

**Negative symptoms:** Blunted affect (including decreased expression of emotion, decreased experience of emotions).

**Overlapping** Avolition, alogia, anhedonia, deterioration in role functioning, personal hygiene

A focus on the non-overlapping symptoms might help distinguish depression from negative symptoms. However, depression and negative symptoms overlap in that they have common features such as reduced activity (reduced social and personal interests), reduced pleasure (anhedonia), reduced motivation (avolition), reduced speech (aloria). All of these features describe a reduced activity without reference to aetiology and they are simply a description of behavior/motivation.

We then performed a longitudinal analysis, but in our data both symptom clusters showed the same pattern over time.

With hindsight, my research presupposes that "Clinical boundaries can be drawn reflecting specific underlying disorders of pathophysiology, with an approximate idea of the location of these pathophysiological entities." This assumption is difficult to underpin (11-13).

If classification is beset by problems related to clinical boundaries, predictive and therapeutic validity, are there other ways of dealing with psychiatric symptoms, such as those encountered in psychosis?

In a dimensional model symptoms can be described not only in terms of presence or not, but also in terms of intensity, frequency and causing more stress, as well as their development over time. A psychosis is a thought to develop, involving a culmination of factors: subclinical symptoms emerge on top of a risk such as age (adolescence), genes (familial risk) and environment (drugs, urban living, being part of a minority). The onset of psychotic disorder can be understood in part as the combination of the causal
impact of different types of subclinical experiences over time: for example negative symptoms predicting psychotic experiences and affective dysregulation impact on the onset of psychotic symptoms, or hallucinations giving rise to delusions. This strongly suggests a network model of the onset of psychotic disorder (12), (14-16).

Correlated psychopathology dimensions seen in patients, are also apparent in risk groups and to a lesser extent in the general population, the difference is their duration, persistence, frequency, and severity (impact on functional outcome).

McGorry et al. first described a dimensional approach in which stages are described: the so called staging model (17). Most of its value is in the treatment of malignancies, where the quality of life and survival are thought to rely on the earliest possible delivery of interventions: oncologists work stepwise, fitting their suggested therapy to the stage of the tumour. A further example is the treatment of hypertension, where the risk of heart disease rather than the disease itself is treated (18).

Where classification lacks continuity – i.e. prognosis about the treatment response and its course is difficult to make - a staging model connects different stages with a different treatment plan and prognosis. Early psychosis and ARMS represents a clinical research paradigm, which has shown that treatment needs are phase specific. Staging may thus be a more useful way of reaching a diagnosis than our classification system. The ideal staging model, however, is clinicopathological: clinical features are augmented by objective measures that are linked to pathophysiology and hence might more accurately guide treatment and prognostic statements. More research in this area is warranted.

**Directions for future research:**

As discussed in this thesis, the adolescent phase is a risk phase for psychosis and the early detection of psychosis and ARMS represents a major progress in psychiatry. Staging has entered psychiatry recently, as it has done in somatic medicine. However, not only psychosis, but most large psychiatric disorders - such as manic-depressive disorder, personality disorders, eating disorders and addiction disorders - emerge in early life: 75% of mental ill-health emerges before the age of 25 years. The disabling and life shortening impact of mental ill-health blight the prime productive years of life with untold misery, and diminishes the social and economic participation of patients and their families in modern life (19).
We also know (just like with psychosis) that some disorders precede others: for example anxiety disorders (in childhood) often precede the later development of a depression; the persistence of symptoms such as in at-risk mental state combined with a lowering in functioning precedes a psychosis. This suggests that an “adolescent-age specific phase/stage approach” is an avenue for further study: every categorical diagnosis can be made dimensional by using symptom counts, symptom duration, symptom severity, degree of impairment, certainty of diagnosis, consensus of multiple diagnoses, and many other strategies without deviating from the framework of current DSM categorical diagnoses (20). A broader focus for early intervention may resolve many of the secondary issues raised by the early psychosis reform process, such as diagnostic uncertainty despite a clear-cut need for care, stigma. Measures for improving the mental health of the young could therefore yield benefits well in excess of costs. There are several ways of approaching this:

1: Using the screening in mental health of adolescents (early detection of ARMS, described in EDIE-NL) as a pilot, developing large, publicly available cohorts of adolescents, referred to mental health, screening for the main psychiatric disorders, and improve low key treatments to reduce stress caused by symptoms, or the symptoms themselves. Our critics might like to consider the comparison of mental wellbeing with dental health; most people would argue that mental wellbeing is more valuable. Preventative dental care is part of our culture and from our childhood we visit the dentist every 6 months for a check-up without giving this a second thought. Why not screening the rest of the head, the brain in this risky phase, in referred patients, between 14-24 years of age?

2: forming a longitudinal cohort with other criteria: referrals are not an all-catching net. Mental health sufferers who do not consult a general practitioner, or who will not be referred by one are missed. Other options can be envisaged by considering that the adolescence phase is a preparation for an adult life; in this phase school/work, developing social relationships outside the primary family is crucial. Hence mental and social health practitioners could focus on adolescents who show a decrease in social functioning (5). It is important to remember that an examination of risk factors of mental ill-health which can influence outcome has revealed that many of them may be reversible. For example, disruption of peer and family networks and vocational drop-out commonly occur around and even before the onset of a first psychotic episode. As dis-engagement with the educational system can lead to behavioural problems, social
exclusion and crime and reduced employment prospects (which in turn make mental ill-health more likely): school-drops and young offenders, or those referred to youth agencies could be screened and followed up: a different cohort altogether: outcome measurements could be diagnoses, but at least social functioning.

This strategy will work best when embedded in a joint (ad)venture between child- and adolescent psychiatry services: a youth model focused on social inclusion, with therapeutics focused at symptom reduction to induce participation in families, relationships as well as school/work, continuously fuelled by data to improve the care.

Questions for this cohort might include:

1. Which symptom domains are precursors for other (more serious) symptom domains?
2. What factors of social functioning are associated with what symptom domains, and how can we influence them?

Early detection of psychosis, and associated study, as described in this thesis, may be a pilot of early detection of other emerging psychiatric disorders in the adolescent life phase.

Limitations

Our results should be considered in the context of some limitations. Most of them have been discussed in the relevant chapters, here we mention the most important limitations of the studies conducted.

Firstly, we need to consider several potential limitations of our studies who include participants: (GROUP, EDIE-NL and EPOS): firstly, a selection bias; participants willing to participate in a demanding study protocol may be different from participants in other less demanding studies, or from subjects refusing to participate in research.

A second limitation is the use of the self-report questionnaire, specifically the Beck Depression Inventory. This may distort the findings by introducing report biases, such as over- or under-reporting of symptoms. Again, caution is therefore required in interpreting the outcomes. Another limitation related to rating depressive symptoms is that we haven’t been able to use throughout all studies a designed questionnaire specifically to assess depressive symptoms in schizophrenia, the Calgary Depression
Rating Scale (CDS), with its proven reliability and validity to measure depression in schizophrenia (21). We have used it to show correlations to be high with BDI, but in hindsight it might have been a good scale to use in ARMS populations, such as EPOS and EDIE.

Thirdly, inter-rater reliability remains a vulnerability in large multisite studies. Although within the GROUP project the inter-rater reliability of the most important diagnostic instruments was assessed. The inter-rater reliability of the diagnostic classification according to DSM-IV as measured by the CASH was satisfactory, based on assessing the concordance between the CASH diagnosis and the diagnosis assessed by the treating clinician. A randomly selected comparison of 65 subjects with a psychotic disorder revealed a difference in diagnosis in only one case. However, the specific inter-rater reliability of negative and depressive symptoms was not assessed, in both EDIE-NL, EPOS and GROUP and this is a limitation of these studies.

A specific limitation of (chapter 6), of the review, is that data were obtained on only 16 of 28 eligible studies. The 12 studies not obtained included 659 patients. Three studies reported correlations between DUP and negative symptoms at 12 to 24 months of follow-up of which 2 were Spearman correlations. Adding data of these two studies in the meta-analysis did not substantially alter the reported correlations of heterogeneity statistics.

A specific limitation of the longitudinal EDIE study (chapter 8) is that our follow-up was limited to 18 months, thereafter important changes in depressive- or negative symptoms 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.
References


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