Emerging symptoms on the pathway to psychosis
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Citation for published version (APA):
Klaassen, M. C. (2013). Emerging symptoms on the pathway to psychosis

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Chapter 1

General Introduction
From clinical practice to research questions

Working in clinical practice with patients raises many relevant research questions. In working with the following patients I encountered certain relevant issues. As a result of taking part in larger research projects, I was able to try to answer these questions, the results of which are presented in this thesis.

The case of Jan:
"During my training as a consultant psychiatrist, I worked on an adult ward for patients with schizophrenia. One of my patients, Jan aged 30, had already experienced two episodes of psychosis, and was admitted to the hospital as he could not function at home between psychotic episodes. Jan rarely left the chair in his room and hardly said a word, due to suspected negative symptoms. During my training I had learnt that depressive symptoms occurred frequently (up to 60%) in schizophrenia, and I wondered whether this was the underlying cause of his behaviour, actions and facial expressions. Jan scored highly on both the negative and the depressive scales and my supervisor agreed that it was worthwhile to try treatment with an antidepressant. After a few weeks we saw noticeable improvements in Jan: he started to move more and began to smile; the depressive symptoms reduced over time.

The diagnostic specificity of negative as opposed to depressive symptoms was not obvious to me and the treatment with an antidepressant seemed to be based on trial and error rather than on firm diagnostics."

My experience with Jan started a fascination with trying to distinguish negative- from depressive symptoms. This topic, i.e. delineating depressive- from negative symptoms, is extensively dealt with in the chapters 5, 7, and 8 of this thesis.

The case of Guus:
"Later in my work, I was trained as a consultant Child and Adolescent Psychiatrist. It was then that I came across Guus, a 16 year old, who had been treated for an anxiety disorder in our outpatient Child- and adolescent psychiatry services. With time, Guus’s functioning deteriorated and he dropped out of school. In fact, he had dropped out of all other social contacts, though he kept contact with his mother. She reported increasingly strange behaviour: Guus had started talking with birds, convinced that he could speak their language. At this point in time, it became apparent that Guus was not suffering from an
anxiety disorder, but had instead developed a psychotic episode as part of the schizophrenia syndrome. Unfortunately he did not improve substantially during antipsychotic treatment and two years later at the age of almost 18, he was transferred to an inpatient mental health care service. The adult ward, with patients aged 18-65 was a source of profound confrontation for him”.

The case of Guus made me wonder whether earlier clinical recognition of the emerging psychotic symptoms would have prevented the unfavourable outcome of Guus’ disorder? This topic, i.e. the early recognition of psychotic phenomena, is extensively dealt with in chapters 2, 3 and 4 of this thesis.

The cases of both Jan and Guus made me wonder about the specificity and validity of diagnostic procedures in psychiatry. Depressive symptoms are mostly considered to be part of a mood disorder, while negative symptoms are seen as part of psychosis, however, they frequently seem to co-occur. Is it feasible to differentiate between them clinically?

Secondly, mental and behavioural problems often manifest themselves well before a final psychiatric diagnosis is made. Parents or patients have a feeling that “something is wrong” long before an official diagnosis of psychosis, or let alone schizophrenia, is established. The question then arises as to whether a better understanding of the nature of these symptoms - negative, depressive as well as positive psychotic - prior to a first episode psychosis enables early detection of emerging symptoms. And furthermore, does this in fact work in daily clinical practice?

All the considerations above have led me to the following main objective of my thesis: gain more clarity in the nature of and relationship between emerging symptoms in the period before and during a first psychotic episode, and especially about the roles of positive, negative as well as depressive symptoms. In short, to investigate “emerging symptoms on the pathway to first episode psychosis.”

**Psychosis and schizophrenia**

Psychosis is considered as a severe psychiatric condition, in terms of both individual and social burden (1). A psychosis diagnosis is based on the presence of positive symptoms; this is partly the case due to the fact they generally can be recognized and quantified
more easily. However, the symptoms of a psychotic disorder can be grouped into four partly interrelated dimensions: positive, negative, cognitive/disorganized and affective symptoms (1-3). Typically, a first episode psychosis becomes manifest in adolescence or young adulthood; in 20-30% of patients it has a chronic course.

Positive symptoms are symptoms that are in excess of or distortions of normal functioning. Commonly patients hear voices (acoustic hallucinations), experience delusions (unrealistic beliefs about which a person is firmly convinced), exhibit bizarre behavior, and/or show formal thought disorder.

Negative symptoms are a core component of schizophrenia and can emerge as early as the prodromal stage of the disorder (4). These symptoms are regarded as a decrease or loss of normal functions (i.e. reduced energy and motivation) and a loss of emotional display of affect. They are commonly described in terms of five dimensions: blunted affect, alogia, anhedonia, avolition and asociality. Cognitive symptoms are not included in the diagnostic criteria of the DSM-IV for schizophrenia, but they are a core feature of schizophrenia symptomatology. They encompass abnormalities in attention, and impairments of executive functioning (5).

Finally, affective symptoms encompass alterations in mood, and may refer to elated (manic) or depressed mood. Depressed mood is a commonly reported symptom in both the phase prior to psychosis, as well as during psychosis (4).

The most well known psychotic disorder is schizophrenia, with an annual incidence rate of about 0.20 per 1000. A life-time prevalence of 0.5-1% (1), (6) indicates the chronic nature of the disorder. Schizophrenia is only diagnosed when illness (psychosis) duration exceeds 6 months. We note here that the broader psychosis spectrum including all psychotic disorders has a lifetime prevalence of 2-3%. (2). Within a first episode psychosis sample only 30-40% will meet criteria for schizophrenia. (7).

The recognition of delusions and hallucinations in psychosis is generally not difficult, but their classification has not been simple. Due to the lack of an aetiopathological basis for diagnosing psychotic disorders, clinicians and researchers alike struggle to diagnose psychiatric conditions such as psychosis in a manner that is etiologically and therapeutically meaningful (8-10). Psychotic disorders are usually classified using the Diagnostic and statistical manual of Mental Disorders, recently updated to its fifth edition (DSM-5). The advantage of the current diagnostic categories is that it facilitates diagnostic agreement (reliability) and communication among practitioners (11). However, classifying symptoms does not imply that the underlying theoretical construct is
necessarily categorical. For example, comorbidity between distinct disorders is high: over 50% of patients with a psychiatric disorder meet criteria for multiple disorders (12). Moreover, some symptom clusters (like Guus’s initial anxiety) are forerunners, (prodromes), of other, more serious symptom clusters. Negative symptoms, or depression symptoms may be forerunners of a psychosis. From a clinical perspective it is sometimes very difficult to discriminate between symptom clusters and a more precise clustering of symptoms can lead to better treatment plan. Indeed, if symptom clusters are potential precursors of more serious psychiatric diagnoses such as psychosis, better knowledge about these precursors is of crucial importance for early intervention.

Schizophrenia is not conceived as a neutral diagnosis, it is partially defined by its poor outcome resulting in pessimism and stigma. Therapeutic efforts have been confined to delayed and palliative care. A revolutionary change in thinking was brought about by the notion that starting earlier with treatment in the first episode of psychosis has a positive effect on the outcome (13). As a result first episode psychosis clinics were set up in the 1980s and much effort was put into detecting young people with a first episode psychosis at the earliest opportunity (7), (14-16), so as to shorten the duration of untreated psychosis (DUP). Early detection and intervention has moved on from this point of detecting patients with a first psychosis, it also became possible to detect people with a high risk of developing a psychosis.

**Early detection and intervention**

Early detection and intervention in psychosis/schizophrenia can have different targets. As only 30-40% of patients with a first episode psychosis actually develop schizophrenia, (7) and duration is one of the most important criteria in reaching a decision, schizophrenia is to some extent a more distal target than psychosis. Yet, generally a psychosis is not a sudden event, but emerges from milder earlier stages. In particular during the prodromal phase patients exhibit symptoms, function less, but are not yet fulfilling the criteria of a psychotic disorder. This phase may well be an even earlier and broader target for intervention for if an intervention could delay or prevent the transition to a psychosis, this would be a breakthrough for reducing the impact of psychotic disorders.
Alison Yung (Early Psychosis Prevention and Intervention Centre in Melbourne, Australia) was the first to define operational criteria for the detection of ultra high risk patients (17), (18). Yung and colleagues conceptualized ARMS as a mixture of social decline, mild-positive psychotic symptoms, mood and anxiety disorders, sleep problems, cognitive impairments. Three subgroups of ARMS have been identified: 1) those patients with attenuated positive psychotic symptoms during the past year; 2) Brief Limited Intermittent Psychotic Symptoms (BLIPS) Group, defined by hallucinations, delusions or formal thought disorders resolving spontaneously within 1 week; and 3) those with a genetic vulnerability: a first-degree relative with a psychotic disorder or a DSM-IV schizotypal personality disorder of the index person, combined with a significant decrease in functioning during the past year. A recent meta-analysis has described the following transition rates: 18% after 6 months of follow-up, 22% after 1 year, 29% after 2 years, and 36% after 3 years. (19).

ARMS studies are typically based on the positive domain of the SOPS; although the majority of ARMS patients will not develop a psychosis, ARMS criteria essentially identify a group of help-seeking young people, who seem to be experiencing symptoms, who are functioning less than healthy controls. Merely focusing on positive symptoms seems to be too limited. Although authors in both retrospective (4), (20) and prospective cohort studies (21), (22) have highlighted the substantial prevalence of negative (up to 40%) and depression symptoms (30–40%) prior to a first episode psychosis, less is known about their role in the ARMS phase.

This thesis

The goal of this thesis is to gain a better understanding of the emerging symptoms on the pathway to psychosis. To this end two central research questions are addressed:
1: Can a better understanding of emerging psychotic symptoms on the pathway to first episode psychosis be acquired and is the early detection of positive psychotic symptoms possible and useful?
2: What role do negative and depressive symptoms play on the pathway to psychosis, and can these two symptom clusters be differentiated from one another?
**Aim 1: acquiring a better understanding of emerging positive symptoms on the pathway to first episode psychosis.**

Screening in the general population at large is not particularly helpful because of the low incidence of schizophrenia. This raises the question as to the whether the screening of genetically pre-disposed individuals (High Risk group) or specific groups of psychiatric patients (Ultra High Risk group) is potentially useful. Chapter 2 focuses on literature dealing this question. An overview of high risk- and ultra-high risk factors (i.e ‘subclinical psychotic symptoms’) for developing a florid first psychotic episode, as well as recommendations for early detection of the at risk state are given.

In chapter 3 the question as to whether a two stage screening method in a secondary mental healthcare setting will detect At Risk Mental State (ARMS) patients is explored. In addition, this approach is compared with a population that was referred to a specialized psychosis clinic.

While the first ARMS studies found transition rates of 40% within a year (23), (24), a lower transition rate of 7-10% has been reported recently (19), (25), (26). ARMS is currently mainly based on positive psychotic symptoms. In addition, ARMS is detected in the adolescence and young adulthood, in which subclinical psychotic symptoms are highly prevalent (up to 30%) (27). Furthermore, subclinical symptoms are transient in 75-90% of the cases (26), (28). A better understanding of the different symptoms and their risk for leading up to psychosis might help to differentiate between true and the false positives.

Chapter 4 presents a literature study of positive phenomena associated with normal adolescent development, as well as positive psychotic phenomena, related to transition to florid psychosis.
**Aim 2: acquiring a better understanding of negative, depressive symptoms, on the pathway to first episode psychosis.**

Genetic factors are assumed to play a role in schizophrenia and other psychotic disorders. Siblings of patients with schizophrenia are at increased risk for psychosis (29-31). Possibly, siblings of schizophrenia patients also show increased presence of affective symptoms. We therefore compared patients with clinical psychosis with their non-psychotic family members, i.e. siblings, with a focus on the presence and development of affective symptoms in and their co-occurrence and association with positive and negative symptoms.

The results are presented in **chapter 5**, which reports an investigation of negative, depressive and positive symptoms in a large cohort of patients with first episode psychosis, their brothers and sisters (siblings) and healthy controls.

Early detection of psychosis is supported by findings about the impact of DUP (Duration of Psychosis) on outcome. The start of the DUP is usually defined as the onset of clear-cut positive psychotic symptoms and its end is taken as the start of antipsychotic treatment. DUP is, as well as ARMS, focused on positive symptoms, whereas negative symptoms are considered a core component of schizophrenia, with prevalence of up to 20-45%. (32), (33).

At the same time negative symptoms are difficult to treat. If a shorter DUP is associated with a reduction in negative symptoms, then the prevention of negative symptoms might be the best way to ameliorate them.

**Chapter 6** reports an investigation of the association between DUP and negative symptoms up to 8 years of follow up utilizing a meta-analysis of individual patient data.

Although the inclusion criteria of ARMS studies are typically based on positive symptoms, both retrospective (4), (20) and prospective cohort studies (21), (22) have highlighted the substantial prevalence of negative (up to 40%) and depression symptoms (30- 40%). The depression and negative symptom clusters are sometimes difficult to distinguish (22), (34-36).
Chapter 7 discusses the question as to whether negative symptoms reported in an ARMS sample can be differentiated from depression symptoms.

As Yung and McGorry (1996) stated, "the prodrome is a process, involving changes in experiences and behavior over time, rather than a simple list of symptoms at any one point". Longitudinal studies are needed to study the role of these changes, in particular the persistence of (subclinical) positive psychotic symptoms, negative and depressive symptoms.

In chapter 8 we report an investigation of the development of depressive and negative symptoms in an ARMS group during 18 months as well as the association with social functioning after 18 months.

To conclude, in chapter 9, the findings of this thesis are summarized. Implications and suggestions for future directions will be made.
Chapter 1

References


