General Introduction

The current ‘Schizophrenia’ concept

The disorder that is nowadays called schizophrenia was already described more than 100 years ago (1,2). Despite considerable progress in the treatment of schizophrenia, the prognosis remains unfavorable with very negative consequences for the affected person and their family, as well as for society due to the considerable economic strain (3). Therefore, most psychotic disorders, and especially schizophrenia, are among the most debilitating mental disorders.

Symptoms

Schizophrenia is characterized by ‘positive’, ‘negative’ and ‘cognitive/disorganized’ symptoms (4). Positive symptoms relate to experiences such as hallucinations, i.e. perceptual experiences not shared by others. For example, delusions are very firmly-held beliefs that are out of keeping with the individual’s cultural or religious origins, that are held with a strong conviction despite reason or proof to the contrary; and a formal thought disorder leads to loss of associations between thought processes, resulting in illogical or incoherent reasoning or speech. Negative symptoms are a core component of psychotic disorders and can emerge as early as the prodromal stage of the disorder (5). They reflect deficit states in which basic emotional and behavioral processes are decreased or absent. These symptoms include anhedonia (lack of pleasure), apathy (diminished ability to initiate and follow through on plans), alogia (reduced quantity or content of speech) and affective flattening (immobile facial expression, monotonous voice tone) (4). Cognitive impairment includes problems in attention and concentration, psychomotor speed, learning and memory, and executive functions (4). Patients often fail to appreciate that their symptoms are caused by illness (6). As a result of these symptoms, many patients lose their capacity to keep a job, to maintain relationships with partners and friends, and/or to take care of themselves and their loved ones.
Epidemiology and course
The first psychotic episode often occurs in adolescence or early adult life; this is an important
time because this is the stage at which a person follows education, finds a partner, and
develops a social network. A psychotic episode can significantly delay any of these devel-
opments. According to a survey of global studies, the averaged incidence (i.e. the number
of new cases per year) was 1.5 per 10,000 persons (7). Worldwide, schizophrenia affects
around 0.3–0.7% of the population at some point in their life (prevalence) (8). In men the
age of onset is on average 5 years earlier than in women (about 18–25 years for men
compared to 25–30 years for women) (9). Schizophrenia is diagnosed 1.4 times more
frequently in males than females (10). Although about 20% of people do well and a few
recover completely (11), individuals with schizophrenia have a shorter average life expectancy
of 10–25 years less compared to the general population (12).

Economic strain
Schizophrenia is among the world’s leading causes of early mortality and long-term disability
(13). This is mainly due to the fact that functional recovery rates have not changed substantially
over the past 25 years, despite advances in pharmacological and psychological treatments
(14,15). Schizophrenia and psychotic disorders are associated with substantial health-related
and economic costs. The main driver of costs are hospitalization and unemployment (16). For
example, in the Netherlands in 2011, the schizophrenia healthcare costs amounted to 735.1
million euros; this was 1.1% of the total costs for Dutch health care in 2011 and 5.3% of the
total healthcare costs that were made for mental disorders (17).

Early detection and intervention in psychosis
In brief, the diagnosis of psychotic disorders is based on internationally accepted criteria
that describe and define the symptoms of the disease; these are published in the recently
updated Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (11).
However, the course, impairments, symptoms and the pathogenesis of psychotic disor-
ders are very diverse. For example, the incidence (i.e. the number of new cases annually)
of schizophrenia is 0.02% in a general population (18). However, according to the DSM-IV,
schizophrenia is only diagnosed when the psychosis exceeds a period of 6 months (19). We
note here that the annual incidence of developing one psychotic symptom is about 100 times
the incidence of schizophrenia (2.5% in a general population) (20). Thus, only one out of
every 100 persons with a psychotic symptom is diagnosed with schizophrenia.
Therefore, the predictive value of a psychotic experience in itself is not very high. For
instance, auditory hallucinations are not necessarily a psychiatric symptom, but can become part of a disorder in the case of attributing an alien origin, power and/or malignant intention to the voices. This implies that psychotic disorders are seen as dimensions (21) and not as separate categorical entities, with different stages and a gradual development (22). This rethinking has led to a paradigm shift in this field, mainly focusing on the psychosis spectrum as a whole and not merely on schizophrenia: this has paved the way for teams focused on early detection and intervention.

The ‘Ultra-High Risk’ stage
Early psychosis clinical services were established in the late 1980s in the Netherlands and in many other places. This was in response to the growing evidence that a long duration of untreated psychosis - i.e. the time from manifestation of the first psychotic symptoms to the initiation of appropriate treatment (23) - is predictive for a poor outcome of psychotic disorders (24). Although establishment of the early psychosis teams resulted in a shorter duration of untreated psychosis, the prognosis was only slightly improved: e.g., within 3 years, 54% of the patients experienced another psychotic episode (25). Apart from this, some patients were referred to the early psychosis departments with mild but distressing psychotic experiences and a decline in social functioning. However, they did not meet the criteria for a full-blown psychotic disorder; this is the so-called ultra-high risk (UHR) stage. This stage is an earlier and broader target for intervention because, if an intervention could delay or prevent the transition to psychosis, this would represent a breakthrough in 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 detection of the UHR stage (26,27). In most cases, the UHR stage is characterized by attenuated psychotic symptoms. A small group has a familial liability (i.e. a first-degree relative with a psychotic disorder, or a DSM-IV schizotypal personality disorder of the index person) for psychotic disorders and/or brief limited intermittent psychotic symptoms (BLIPS; i.e. a psychosis lasting shorter than 1 week that resolves spontaneously). All groups are characterized by increased social isolation, functional decline and help-seeking for co-morbid axis-1 and axis-2 disorders (28,29). The UHR criteria can be assessed using the Comprehensive Assessment of At-Risk Mental States (CAARMS) instrument (28). A meta-analysis from 2012 reported transition rates of up to 36% after 3 years (30).

The Early Detection and Intervention Evaluation in the Netherlands
For most of the early detection teams, patient recruitment relies mainly on suspicion of a psychotic development and referral to a highly specialized tertiary medical research center. However, a screening method is reported to have detected more patients with an UHR of developing psychosis (31). This suggests that untrained community health caretakers, who
are the most important providers, can miss many psychotic developments. The Dutch Early Detection and Intervention Evaluation (EDIE-NL, see Chapter 2) is the first study to screen in a general help-seeking population (aged 14–35 years) entering secondary mental healthcare settings in the Netherlands. The main aims of that study were to identify the UHR group in routine mental health care, to offer them proactive/preventive cognitive behavior therapy for UHR (CBTuhr), and to guide them through a critical phase of life whereby the transition to a first-episode of psychosis is prevented, in an adequate and (cost-) effective manner.

Outline of this thesis

Chapter 1 describes the background of this work. Chapter 2 presents the protocol of the EDIE-NL study, including its aims, sampling procedure, diagnostic instruments, randomization protocol, quality procedures and data analysis. In Chapter 3 the development and implementation of the 16-item version of the Prodromal Questionnaire (PQ-16) in routine mental health care is described. It is acknowledged that screening detects more patients at the entry point to mental health services, because combining different risk factors (e.g. young age, help-seeking, and co-morbid psychiatric problems such as anxiety, depression or trauma) allows to select a highly enriched sample. Earlier, the most widely used screening list was the Prodromal Questionnaire 92-item version. However, to make screening more efficient in daily practice, a short screener was developed (the PQ 16). The sensitivity and specificity of the PQ-16 at an optimal cut-off point has been determined. Chapter 4 examines the association between UHR status and co-morbidity (in particular anxiety and depression) with respect to differences between male and female patients. Chapter 5 reports on the 4-year outcome of UHR symptoms in patients that did and did not receive cognitive behavior therapy (CBTuhr) to delay or even prevent transition to psychosis. The 18-month follow-up results of the EDIE-NL study demonstrated that CBTuhr halved the incidence of psychosis. The short-term results (i.e. 1.5 years after baseline) of the cost-effectiveness and cost-utility of preventive CBT are presented in Chapter 6. Following the results of that study, Chapter 7 investigated the longer term cost-effectiveness and cost-utility of CBT for the prevention of a first episode of psychosis. Chapter 8 examines the association between childhood abuse and clinical and functional outcome at 4-year follow-up. In Chapter 9 a prognostic prediction model is described that discriminates between three risk groups, each with a different risk for transition to psychosis. In conclusion, Chapter 10 summarizes the key findings of the work presented in this thesis. Important limitations are addressed, implications are discussed and some suggestions are made for future research.
References


