Early detection of psychosis; why should we care?

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CHAPTER 1

General introduction

A psychotic disorder, and specifically schizophrenia, has long been seen as a disease, automatically combined with a decline in functioning over time. Recently, a more optimistic approach has been emerged, which is more focused on psychosis. The rationale for this approach relies partly on the positive results of early diagnosing and treating people either with an emerging psychosis or a previous one. The Duration of a (first) Untreated Psychosis (DUP) appears to be a key factor in the optimistic perspective: the shorter the DUP the better the short and long term outcome. Because the term DUP covers a number of different elements - the reason for the delay may reside within the patient, the mechanisms of referral, or the recognition by the treating team, it is difficult to explain the true nature of its relationship with outcome. The start of the DUP usually is defined by the onset of clear cut positive psychotic symptoms and its end is defined by the commencement of antipsychotic treatment.

The aim of this dissertation is to add to the knowledge of DUP, in relation to symptomatology (patient delay factor), and in relation to pathways to care (referral delay), and treatment delay caused by the mental health sector itself. It encompasses all the known elements of DUP.

INCIDENCE AND PREVALENCE

Our focus is on patients with a diagnosis of psychosis. In particular we consider here non-affective psychotic disorders which include the categorical diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder or psychosis not explicitly categorized (psychosis not otherwise specified).

According to a recent meta-analysis, the yearly median incidence of non-affective psychotic disorder is about 15 per 100,000 inhabitants (1). Geographical differences in incidence rates are attributed to the distribution of risk factors such as growing up in urban environment, migration, social exclusion, and alcohol and drug abuse (1). These differences cannot be attributed to differences in the characteristics of the research design like diagnostic criteria, methodological quality of the study or age cut off points. The incidence in the Netherlands may therefore differ from that in other countries. The yearly prevalence of psychotic disorders is about 4.6 per 1,000 inhabitants (1) which is 30-fold higher than the incidence rate.

Males have a greater chance of developing a psychotic disorder than females and are commonly diagnosed during adolescence (aged 14-23 years). The age range at onset for males is 5 years earlier than for females (2) (about 18-25 compared to about 25-30 for females). The gender distribution of psychotic disorder is 1.4 males : 1 female (1). There is a subgroup of women (approximately 5%) with a late onset of psychosis at the age of 40 or older (2;3). The protective effect of oestrogen is

cited as a possible explanation for the difference in the age of onset of psychoses between males and females.

PROGNOSIS OF PSYCHOSIS; HISTORICAL PERSPECTIVE

Since the time of Kraepelin the prognosis of schizophrenia has been considered to be poor. In 1889 Kraepelin described the process of deterioration in schizophrenia as a fundamental feature of the disorder, which was captured by the term dementia praecox (4). Bleuler endorsed Kraepelin's definition of the deteriorating clinical state but emphasized that course and outcome were not homogeneous amongst all patients (5). Bleuler also conceptualized milder forms of the disease, e.g. those preventing people from achieving important goals in life, but still allowing a relatively quiet or isolated existence. Given the variable nature of the disorder, clinicians attempted to reduce its heterogeneity by distinguishing subtypes. The traditional subtypes of paranoid, undifferentiated, disorganized, and catatonic schizophrenia were defined on the basis of alleged qualitative differences in psychopathology despite the absence of validating scientific evidence concerning treatment response, long-term outcome, pathophysiological processes, or genetics (6)The chronic course has been the basis of the schizophrenia concept for a long time even up to the 21th century. Sawa and Snyder expressed this pessimistic view in a general review in Science in 2002 and noted that when symptoms of schizophrenia occur, usually in young adulthood, they persist for the entire lifetime and are almost totally disabling (7).

Fortunately, recent meta-analyses show that prognosis is much better than was previously assumed. At the end of the 20th century Hegarty et al. found that 40.2% of more than 50,000 patients (8) were considered improved after a mean follow-up of 6 years. In 2006 Menezes et al. reported good outcomes in 42.2% of cases representing 4100 patients from 37 studies with a mean follow-up of 3 years (9).

In 1997 Richard Jed Wyatt et al. conducted a review of schizophrenia patients in the transition periods before, during and after the introduction of antipsychotic medication (10). Wyatt postulated that antipsychotics treat active psychotic symptoms as well as prevent deterioration. He further promoted the neurotoxicity hypothesis: "while psychosis is undoubtedly demoralizing and stigmatizing, it may also be biologically toxic" (10). The notion that psychosis untreated by antipsychotics might be toxic to the brain was bolstered by longitudinal studies of first episode schizophrenia samples during the same period. Loebel and Lieberman, for example, noted that longer duration of untreated psychosis correlated with poorer outcome and higher relapse rates (11). The linking of the duration of untreated psychosis (DUP) to the outcome opens the perspective of improving the course of the disease. But it proved harder to establish a causal association between long duration of untreated psychosis and bad outcome. A test of the hypothesis of a neurotoxic effect of psychosis requires randomized controlled trials delaying treatment in one, and initiating treatment immediately in the other and measuring functional outcome and brain development longitudinally, something which is difficult to justify ethically.

In the beginning of the 21th century McGlashan hypothesized that synaptic plasticity instead of neurotoxicity is the mediating process responsible for prognosis (4). The synaptic plasticity hypothesis supposes that the neuropathology of schizophrenia centres around a significantly reduced neuropil, i.e. the synaptic syncytium between neurons (12). McGlashan poses further that the deficits of psychosis may result from attenuated or reduced synaptic plasticity. The hypothesis is that a withdrawal from daily life leads to a reduced synaptic activity. The main basis for this hypothesis of reduced connectivity is the fact that most deterioration occurs in the early stages of the illness including the prodromal phase (4). Social withdrawal is characteristic for a psychotic disorder and may probably be one of the key negative symptoms. Negative symptoms generally appear before the appearance of positive symptoms and the first break of psychosis (2). In addition, the hypothesis assumes that psychotic symptoms, particularly positive symptoms, may reflect a (psycho)pathological process that may also cause deterioration. Recent imaging studies have shown a reduction in neuronal membrane integrity during the prodrome and the first stages of psychosis (13;14), but antipsychotics may have some protective effect (15;16). Any poor outcome is attributed to a toxic effect of psychosis or changes prior to psychosis, so that early intervention seems an important potential factor of prevention.

The rethinking of schizophrenia as a disease that might be treatable and even curable was not only influenced by the outcome of meta-analyses, but also by the early intervention paradigm, which mainly focuses on the psychosis spectrum as a whole and not merely on schizophrenia. Early detection and intervention teams are implemented based on the hypothesis that the DUP-outcome association is causal and the course of a psychosis may be influenced by early intervention. Many current developments, such as setting standards to treatment, staging and profiling, moving step-by-step towards better treatment results as implemented by guidelines, have been largely influenced by the approach of early intervention (17-19). Although it has not been established whether shortening DUP actually affects prognosis, these reflections and insights led to the first Early Psychosis Prevention and Intervention Center (EPPIC) in Melbourne in 1988 (20). Early detection and intervention programs have now been implemented all over the world, based on the widely accepted idea that untreated psychosis should be as short as possible.

DURATION OF UNTREATED PSYCHOSIS AND ITS RELATION WITH OUTCOME

A large number of studies have examined the relationship between Duration of Untreated Psychosis (DUP) and outcome. DUP is defined as the time from the manifestation of the first positive psychotic symptoms to the initiation of appropriate treatment (21). Shorter DUP has been shown to be associated with earlier and better level of remission (22-24), lower relapse rates (25;26), less cognitive deterioration (27), less positive symptoms (28-31) and better social functioning (32;33). Furthermore, an association has been reported of long DUP and self harm (34). The impact of a shorter DUP on outcome is most pronounced in the initial months following illness onset (35). These empirical data support the deleterious consequence of un-

treated psychosis mentioned above. Although DUP seems to be associated with clinical outcome in a causal way, the causality remains disputed as it is uncertain whether the shortening of DUP will lead to better outcome.

DUP is entirely focused on positive symptoms, which play a big part in diagnosing psychosis. However, another clinical dimension, known as negative symptoms, also has a strong association with outcome. It has been shown that negative symptoms are related to a poor functional outcome (36), cognitive deficits (37), social dysfunction and a poor quality of life (38-40). The association between DUP and negative symptoms is less well established than the association between DUP and positive symptoms. A few studies show an association between longer DUP and more severe and more persistent negative symptoms (41;42) although the results are inconclusive due to a lack of evidence for the longer term follow-up. Negative symptoms are usually present early in the illness and are less responsive to treatment than positive symptoms. Besides, they play a minor role in deciding whether or not a person suffers from a psychosis. Studies on the course of psychosis demonstrate that the first symptoms to appear are depressive and negative even before the appearance of positive psychotic symptoms (2). The prevalence of negative symptoms in short-term follow-up studies (up to 2.5 years) is about 45% (36;43;44), and in longer term studies (7.5-10 years) 20-30% (45). There are no data on the association of DUP and the presence of negative symptoms in the long term.

There are two meta-analyses reporting on the association between DUP and negative symptoms (46;47). Whilst making a valuable contribution, both share several limitations. These analyses, based only on published data, used combined correlations calculated by different techniques, for example parametric in some studies and non-parametric in others. Most studies included in these meta-analyses used DUP as a dichotomous variable: short DUP versus long DUP. However in one study ‘short’ is defined as less than 6 months while in another study as less than one year. So the criterion for setting a cut-off point between short and long DUP is ill-defined. The relationship between DUP and outcome may not be linear along the range of DUP. We think, when examining the relationship between DUP and outcome and a potential critical period, DUP should be used as a continuous variable. Based on this knowledge it would be interesting to know the strength of the association between DUP and the level of negative symptoms at various lengths of follow-up.

COMPONENTS OF TREATMENT DELAY

All the available evidence indicates that shortening DUP is of great importance for prognosis. Nevertheless, several factors might contribute to treatment delay. Norman et al. describe two components of DUP: first the delay caused by the patients contacting health professionals and second the delay caused by mental health care services after the first contact has already been made (48). Both delay components appear to be of equal importance. Patients who had their first contact with the services before the first onset of psychosis had a substantial longer service delay compo-

nent. This also holds true for those patients who had their first contact around their first onset of psychosis (48).

Brunet et al. (49) defined DUP as the sum of three components;
1. Delay in help-seeking.
2. Delay in referral e.g. by a general practitioner.
3. Delay in recognition by mental health care services (MHS).

Each of the three components was found to account for 33% of overall DUP in a study of 80 participants from the inner city of Birmingham (49). Both Norman et al. and Brunet et al. argue that efforts to minimize the effects of shortening DUP should be primarily targeted at a reduction of the service delay (48;49). Recently, a large scale multi-centre study of pathways to care also demonstrated that a substantial proportion of DUP was caused by delay after first contact by mental health care services (50). The evidence suggests that mental health care services do not recognize psychosis properly, at least in England and Canada.

EXAMPLES OF EARLY DETECTION STUDIES:

A few studies have examined interventions which aim to reduce DUP. The Scandinavian TIPS study (early Treatment and Intervention in PsychosiS) consisted of intensive public educational campaigns with information about early psychosis through cinemas, television, schools and newspapers and the comparisons were realised by sending specialised early detection teams to only one region (51). The TIPS study showed that an early detection program does indeed shorten patient delay and referral delay. The overall median DUP was reduced from 12 weeks to 4 weeks. Patients with shorter DUP exhibited neither faster remission nor better clinical outcome after one year follow-up, though they suffered less from severe negative symptoms after 2 and after 5 years of follow-up and they had significantly less suicidal thoughts (52;53). It should be noted that when the intensity of the information campaign decreased, DUP increased again from 4 weeks to 13 weeks.

Another early detection form is targeted at potential referrers. The BiRmingham Early Detection In untREated psychosis Trial (REDIRECT) explored whether an educational intervention targeted at general practitioners (GPs) increased the GP referral rate of first episode psychotic patients to early intervention services (54). The educational intervention consisted of addressing GP knowledge, skills, and attitudes. Control GP's received an alternative educational program, for instance, in cognitive behavioral therapy. It was concluded that GP training in first-episode psychosis is insufficient to alter referral rates to early-intervention services or to reduce the duration of untreated psychosis.

In contrast the Lambeth Early Onset Crisis Assessment Team Study (LEO CAT) showed that educating GPs did improve detection and referral rates of first episode psychosis patients. The team compared the effectiveness of a GP education pro-

gram with direct access to an early detection team on reducing treatment delay with treatment as usual (55).

The work discussed above suggests that patient delay and referral delay can be shortened with an appropriate intervention for a sufficiently long period. There are no suitable interventions known to shorten delay caused by mental health care services. As we have to be able to rely on patients entering mental health care services receive appropriate treatment, shortening this component of treatment delay is of high importance. It would therefore be appropriate to investigate how mental health care service delay can be improved.

OUTLINE OF THIS THESIS

We examined the incidence of non-affective psychotic disorders in the Netherlands in chapter 2. Medical records of patients who were referred to mental health care services in Friesland and Twente in 2002 were screened for psychotic symptoms and clinical diagnoses at baseline and after 30 months of follow up.

In addition, these records were screened for treatment for psychotic symptoms in order to establish to what extent patients with psychotic symptoms received treatment for their psychotic symptoms. Results are presented in chapter 3.

A meta-analysis using individual patient data of the association between DUP and negative symptoms up to 8 years of follow up is described in chapter 4. This chapter also reports the critical period of DUP regarding negative symptoms.

In order to examine the pathways to care and the causes of treatment delay, we conducted a study in the province of Friesland and the city of Amsterdam. Chapter 5 describes treatment delay of first episode psychotic patients caused by patient delay, referral delay and mental health care service delay and the role of urbanicity and migration in these pathways to care.

The effect of the implementation of a self-assessment questionnaire during the intake procedure of mental health care services, the Community Assessment of Psychic Experiences (CAPE-42), on improving the detection of first episode psychotic patients by mental health care services is evaluated in chapter 6. Sensitivity and specificity of the CAPE-42 at an optimal cut-off point are determined.

In chapter 7 the main findings are summarized and discussed. Also some additional limitations and validity issues of the studies described in this thesis will be discussed and implications for clinical practice and further research are presented.

REFERENCE LIST

(1) McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med 2004; 2:13.

(2) DeLisi LE. The significance of age of onset for schizophrenia. Schizophr Bull 1992; 18(2):209-215.

(3) Hafner H. Onset and early course as determinants of the further course of schizophrenia. Acta Psychiatr Scand Suppl 2000;(407):44-48.

(4) McGlashan TH. Is active psychosis neurotoxic? Schizophr Bull 2006; 32(4):609-613.

(5) Bleuler M. Schizophrenic deterioration. 1. Br J Psychiatry 1983; 143:78-79.

(6) Lieberman J. Signs and symptoms. What can they tell us about the clinical course and pathophysiologic processes of schizophrenia? Arch Gen Psychiatry 1995; 52(5):361-363.

(7) Sawa A, Snyder SH. Schizophrenia: diverse approaches to a complex disease. Science 2002; 296(5568):692-695.

(8) Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C, Oepen G. One hundred years of schizophrenia: a meta-analysis of the outcome literature. Am J Psychiatry 1994; 151(10):1409-1416.

(9) Menezes NM, Arenovich T, Zipursky RB. A systematic review of longitudinal outcome studies of first-episode psychosis. Psychol Med 2006; 36(10):1349-1362.

(10) Wyatt RJ, Green MF, Tuma AH. Long-term morbidity associated with delayed treatment of first admission schizophrenic patients: a re-analysis of the Camarillo State Hospital data. Psychol Med 1997; 27(2):261-268.

(11) Loebel AD, Lieberman JA, Alvir JM, Mayerhoff DI, Geisler SH, Szymanski SR. Duration of psychosis and outcome in first-episode schizophrenia. Am J Psychiatry 1992; 149(9):1183-1188.
(12) Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? J Psychiatr Res 1982; 17(4):319-334.

(13) Wood SJ, Berger GE, Lambert M, Conus P, Velakoulis D, Stuart GW et al. Prediction of functional outcome 18 months after a first psychotic episode: a proton magnetic resonance spectroscopy study. Arch Gen Psychiatry 2006; 63(9):969-976.

(14) Wood SJ, Pantelis C, Velakoulis D, Yucel M, Fornito A, McGorry PD. Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. Schizophr Bull 2008; 34(2):322-329.

(15) Lieberman JA, Phillips M, Gu H, Stroup S, Zhang P, Kong L et al. Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. Neuropsychopharmacology 2003; 28(5):995-1003.

(16) Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS et al. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 2005; 62(4):361-370.

(17) Rose VL. APA practice guideline for the treatment of patients with schizophrenia. Am Fam Physician 1997; 56(4):1217-1220.

(18) CBO. Update multidisciplinaire richtlijn schizofrenie. 2010.
(19) National Institute for Health and Clinical Excellence. NICE guideline schizophrenia. 2010.

(20) McGorry PD, Edwards J, Mihalopoulos C, Harrigan SM, Jackson HJ. EPPIC: an evolving system of early detection and optimal management. Schizophr Bull 1996; 22(2):305-326.

(21) Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. Arch Gen Psychiatry 2005; 62(9):975-983.

(22) Malla AK, Norman RM, Manchanda R, Ahmed MR, Scholten D, Harricharan R et al. One year outcome in first episode psychosis: influence of DUP and other predictors. Schizophr Res 2002; 54(3):231-242.

(23) Simonsen E, Friis S, Haahr U, Johannessen JO, Larsen TK, Melle I et al. Clinical epidemiologic first-episode psychosis: 1-year outcome and predictors. Acta Psychiatr Scand 2007; 116(1):54-61.

(24) Wunderink A, Nienhuis FJ, Sytema S, Wiersma D. Treatment delay and response rate in first episode psychosis. Acta Psychiatr Scand 2006; 113(4):332-339.

(25) Altamura AC, Bassetti R, Sassella F, Salvadori D, Mundo E. Duration of untreated psychosis as a predictor of outcome in first-episode schizophrenia: a retrospective study. Schizophr Res 2001; 52(1-2):29-36.

(26) de Haan L, Linszen DH, Lenior ME, de Win ED, Gorsira R. Duration of untrea-

ted psychosis and outcome of schizophrenia: delay in intensive psychosocial treatment versus delay in treatment with antipsychotic medication. Schizophr Bull 2003; 29(2):341-348.

(27) Amminger GP, Edwards J, Brewer WJ, Harrigan S, McGorry PD. Duration of untreated psychosis and cognitive deterioration in first-episode schizophrenia. Schizophr Res 2002; 54(3):223-230.

(28) Black K, Peters L, Rui Q, Milliken H, Whitehorn D, Kopala LC. Duration of untreated psychosis predicts treatment outcome in an early psychosis program. Schizophr Res 2001; 47(2-3):215-222.

(29) Bottlender R, Sato T, Jager M, Wegener U, Wittmann J, Strauss A et al. The impact of the duration of untreated psychosis prior to first psychiatric admission on the 15-year outcome in schizophrenia. Schizophr Res 2003; 62(1-2):37-44.

(30) Larsen TK, Moe LC, Vibe-Hansen L, Johannessen JO. Premorbid functioning versus duration of untreated psychosis in 1 year outcome in first-episode psychosis. Schizophr Res 2000; 45(1-2):1-9.
(31) Norman RM, Malla AK, Manchanda R. Early premorbid adjustment as a moderator of the impact of duration of untreated psychosis. Schizophr Res 2007; 95(1-3):111-114.

(32) Drake RJ, Haley CJ, Akhtar S, Lewis SW. Causes and consequences of duration of untreated psychosis in schizophrenia. Br J Psychiatry 2000; 177:511-515.

(33) Harris MG, Henry LP, Harrigan SM, Purcell R, Schwartz OS, Farrelly SE et al. The relationship between duration of untreated psychosis and outcome: an eight-year prospective study. Schizophr Res 2005; 79(1):85-93.

(34) Upthegrove R, Birchwood M, Ross K, Brunett K, McCollum R, Jones L. The evolution of depression and suicidality in first episode psychosis. Acta Psychiatr Scand 2009.

(35) Drake RJ, Haley CJ, Akhtar S, Lewis SW. Causes and consequences of duration of untreated psychosis in schizophrenia. Br J Psychiatry 2000; 177:511-515.

(36) Malla AK, Norman RM, Takhar J, Manchanda R, Townsend L, Scholten D et al. Can patients at risk for persistent negative symptoms be identified during their first episode of psychosis? J Nerv Ment Dis 2004; 192(7):455-463.

(37) Heydebrand G, Weiser M, Rabinowitz J, Hoff AL, DeLisi LE, Csernansky JG. Correlates of cognitive deficits in first episode schizophrenia. Schizophr Res 2004; 68(1):1-9.

(38) Addington J, Addington D. Premorbid functioning, cognitive functioning, symptoms and outcome in schizophrenia. J Psychiatry Neurosci 1993; 18(1):18-23.

(39) Petersen L, Thorup A, Oqhlenschlaeger J, Christensen TO, Jeppesen P, Krarup G et al. Predictors of remission and recovery in a first-episode schizophrenia spectrum disorder sample: 2-year follow-up of the OPUS trial. Can J Psychiatry 2008; 53(10):660-670.

(40) Schmitz N, Malla A, Norman R, Archie S, Zipursky R. Inconsistency in the relationship between duration of untreated psychosis (DUP) and negative symptoms: sorting out the problem of heterogeneity. Schizophr Res 2007; 93(1-3):152-159.

(41) Perkins D, Lieberman J, Gu H, Tohen M, McEvoy J, Green A et al. Predictors of antipsychotic treatment response in patients with first-episode schizophrenia, schizoaffective and schizophreniform disorders. Br J Psychiatry 2004; 185:18-24.

(42) Simonsen E, Friis S, Haahr U, Johannessen JO, Larsen TK, Melle I et al. Clinical epidemiologic first-episode psychosis: 1-year outcome and predictors. Acta Psychiatr Scand 2007; 116(1):54-61.

(43) Malla AK, Takhar JJ, Norman RM, Manchanda R, Cortese L, Haricharan R et al. Negative symptoms in first episode non-affective psychosis. Acta Psychiatr Scand 2002; 105(6):431-439.

(44) Pogue-Geile MF, Harrow M. Negative symptoms in schizophrenia: their longitudinal course and prognostic importance. Schizophr Bull 1985; 11(3):427-439.

(45) Herbener ES, Harrow M. Longitudinal assessment of negative symptoms in schizophrenia/schizoaffective patients, other psychotic patients, and depressed patients. Schizophr Bull 2001; 27(3):527-537.

(46) Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. Arch Gen Psychiatry 2005; 62(9):975-983.

(47) Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry 2005; 162(10):1785-1804.

(48) Norman RM, Malla AK, Verdi MB, Hassall LD, Fazekas C. Understanding delay in treatment for first-episode psychosis. Psychol Med 2004; 34(2):255-266.

(49) Brunet K, Birchwood M, Lester H, Thornhill K. Delays in mental health services and duration of untreated psychosis. Psychiatric Bulletin 2007;(31):408-410.

(50) Marshall M, Husain N., Warwurton J, Birchwood M, Lester H, Fowler D et al. Delays in the pathway to care for a first episode of psychosis: an analysis of the components of duration of untreated psychosis from the Nation Eden Study. Early Intervention in Psychiatry 2008; 2 (suppl.1):A18.

(51) Johannessen JO, McGlashan TH, Larsen TK, Horneland M, Joa I, Mardal S et al. Early detection strategies for untreated first-episode psychosis. Schizophr Res 2001; 51(1):39-46.

(52) Friis S, Vaglum P, Haahr U, Johannessen JO, Larsen TK, Melle I et al. Effect of an early detection programme on duration of untreated psychosis: part of the Scandinavian TIPS study. Br J Psychiatry Suppl 2005; 48:s29-s32.

(53) Johannessen JO, Joa I, Auestad B, Haahr U, Larsen TK, Melle I et al. First-episode psychosis patients recruited into treatment via early detection teams versus ordinary pathways: course and health service use during 5 years. Early Interv Psychiatry 2011; 5(1):70-75.

(54) Tait L, Lester H, Birchwood M, Freemantle N, Wilson S. Design of the BiRmingham Early Detection In untREated psyChosis Trial (REDIRECT): cluster randomised controlled trial of general practitioner education in detection of first episode psychosis [ISRCTN87898421]. BMC Health Serv Res 2005; 5(1):19.

(55) Power P, Iacoponi E, Reynolds N, Fisher H, Russell M, Garety P et al. The Lambeth Early Onset Crisis Assessment Team Study: general practitioner education and access to an early detection team in first-episode psychosis. Br J Psychiatry Suppl 2007; 51:s133-s139.

CHAPTER 2

De administratieve incidentie van niet-affectieve psychosen in Friesland en Twente

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SAMENVATTING

ACHTERGROND

Onderzoek naar risicofactoren van schizofrenie leidde tot hernieuwde aandacht voor geografische verschillen in de incidentie en geslachtsverdeling van schizofrenie. De GGZ geregistreerde incidentie van niet-affectieve psychotische stoornissen bij mannen en vrouwen in diverse regio's in Nederland is niet bekend.

DOEL

Vaststellen van de GGZ- geregistreerde jaarincidentie naar geslacht in 2002 van niet-affectieve psychotische stoornissen in Friesland en Twente.

METHODE

De dossiers van alle volwassenen met een eerste zorgcontact in 2002 (n=6477) in twee GGZ instellingen in Nederland zijn gescreend op psychotische symptomen. Alle patiënten met psychotische symptomen (N=242) zijn geincludeerd en hun klinische diagnose geregistreerd. Dertig maanden later is de meest recente diagnose opnieuw geregistreerd.

RESULTATEN

Bij 75 patiënten werd de diagnose niet-affectieve psychotische stoornis gesteld, waarbij deze diagnose na dertig maanden gehandhaafd bleef, een incidentie van 2,2/10.000 inwoners. De man-vrouw verhouding was 1,8:1. De incidentie van niet-affectieve psychosen verschilde niet significant in de beide onderzoeksgebieden.

CONCLUSIE

De gevonden incidentie komt overeen met de incidentie die in eerdere Nederlandse studies gevonden werd en ligt op het 75e percentiel van de cumulatieve incidentie in een internationale review.

Trefwoorden: incidentie, detectie. Eerste psychose, niet-affectieve psychose, schizofrenie.

INLEIDING

ACHTERGROND

Geografische verschillen in de incidentie van schizofrenie zijn weliswaar al lang bekend maar bij de interpretatie van de gegevens zijn deze verschillen dikwijls veronachtzaamd (Crow, 2000). De algemene visie was dat de incidentie van schizofrenie over de hele wereld ongeveer gelijk was en niet of nauwelijks werd beïnvloed door omgevingsfactoren, geslacht, etniciteit of andere demografische variabelen. Grote datasets, zoals die van de WHO Ten Country Study tonen weliswaar duidelijke verschillen in de incidentiecijfers over de wereld, maar deze werden vooral toegeschreven aan vertekeningen door de onderzoeksopzet en niet aan werkelijke geografische incidentieverschillen (Jablensky,1992, Crow, 2000). Een nieuw gezichtspunt vormde de systematische review van McGrath (2004). Hij toonde aan dat de gevonden geografische verschillen in incidentie wel degelijk substantieel waren. Mogelijk zouden deze verschillen kunnen worden verklaard door de uiteenlopende distributie van risicofactoren zoals urbanisatiegraad, migratie, sociale exclusie, alcohol en drugmisbruik. In deze review, met 55 studies uit 25 landen, varieerde de incidentie van 0,77 tot 4,3 per 10.000 inwoners, de mediaan was 1,52/10.000 inwoners. De incidentie veranderde niet significant wanneer werd gecorrigeerd voor mogelijke beïnvloedende factoren, zoals diagnostische criteria, onderzoeksmethode, afkappunt voor leeftijd of kwaliteit van de studie. Als gevolg van dit inzicht kan de incidentie van schizofrenie in Nederland niet zonder meer worden afgeleid uit gegevens van andere landen. Het is goed denkbaar dat risicofactoren in Nederland anders gedistribueerd zijn dan elders in de wereld, zoals het gebruik van cannabis, immigratie, sociale exclusie en urbanisatie.

In tabel 1 wordt een overzicht gegeven van de Nederlandse studies die de ggz-incidentie en de geslachtsverdeling van psychotische stoornissen in Nederland beschrijven (Giel, 1980, Selten, 2001, Wunderink, 2006). In deze studies wordt een incidentie gevonden die varieert van 1,12 tot 4,0 per 10.000 inwoners. Er zijn geen recente studies beschikbaar die zich primair richten op de ggz-incidentie van psychotische stoornissen in Nederland, genoemde studies hadden allemaal een andere primaire doelstelling. De doelstelling van de in dit artikel beschreven studie is het vaststellen van het aantal geregistreerde patiënten met een niet-affectieve psychotische stoornis onder alle eerste aanmeldingen in twee rurale GGZ regio's in Nederland, te onderscheiden naar geslacht en leeftijd. Een nevendoelstelling is te bekijken of de incidentie tussen beide regio's varieert, onder andere vanwege de enigszins uiteenlopende urbanisatiegraad.

METHODE

ONDERZOEKSGEBIED

De studie is uitgevoerd bij twee GGZ instellingen met een totaal verzorgingsgebied van 1,028 miljoen inwoners. Het verzorgingsgebied van GGZ Friesland bedroeg op 1 januari 2002 636.000 inwoners, met 189 inwoners per km². Het inwonertal in het verzorgingsgebied van Mediant, Twente telde op dat moment 392.000 inwoners met 751 inwoners per km².

PATIËNTEN

De medische dossiers van alle patiënten tussen 18-45 jaar die een eerste zorgcontact hadden met één van de twee GGZ instellingen in 2002 werden gescreend op gerapporteerde psychotische symptomen. Deze psychotische symptomen zijn ontleend aan de symptomen zoals beschreven onder paragraaf A in de sectie “Schizofrenie en andere psychotische stoornissen” van de DSM-IV (American Psychiatric Association, 1994): wanen, hallucinaties, onsamenhangende spraak en ernstig chaotisch of katatoon gedrag(1). Alle beschikbare documenten met betrekking tot de eerste zes maanden van de behandeling werden hiervoor gebruikt. Niet geïncludeerd in de screening werden patiënten die al eerder waren behandeld wegens psychotische symptomen; wel gescreend werden patiënten die eerder voor een ander probleem werden behandeld. Geselecteerd voor het onderzoek werden alle patiënten bij wie in het medische dossier gerapporteerd werd over tenminste 1 van de 4 psychotische symptomen. Bij deze patiënten werd de toegekende klinische diagnose geregistreerd, en na 30 maanden follow-up opnieuw. Alleen die patiënten bij wie de toegekende klinische diagnose aanvankelijk een niet-affectieve psychotische stoornis was (DSM-IV: schizofrenie, schizofreniforme stoornis, kortdurende psychose, schizo-affectieve stoornis, waanstoornis of psychotische stoornis niet anders omschreven), en bij wie dat na dertig maanden follow-up nog het geval was, werden meegenomen in de berekening van de administratieve incidentie.

STATISTISCHE ANALYSE

De betrouwbaarheidsintervallen van de incidenties werden berekend volgens de gebruikelijke formule, met als assumptie dat de binomiale verdeling normaal verdeeld is (zie Brown e.a., 2001).

Tabel 1. Overzicht van studies naar incidentie van niet- affectieve functionele psychosen in Nederland

	Incidentie/ 10.000 inw.	Incidentie/ 10.000 inw. mannen	Gem leeftijd	Incidentie/ 10.000 inw. vrouwen	Gem leeftijd	M:V ratio	N	Leeftijd	Diagnostisch instrument	Onder-zoeks-periode
Giel (1980)	**1,12** at risk functionele psychosen	**0,88** at risk functionele psychosen		**1,37** at risk functionele psychosen		0,64:1	Pop van 216.228 inw Provincie Groningen & Drenthe n=47	15-44	PSE DSM-III	1978-1979
Selten (1999)	**3,5**/10.000 at risk (95% CI 3.0-4.0)	126/264510 = **4,8**/10.000 at risk	28,3 jaar (SD 9,2)	55/251217= **2,2**/10.000 at risk	32,0 jaar (SD 9,5)	2,2:1	Pop 258.493 inw. at risk n=181 in 2 jr	15-54	CASH & IRAOS	1997-1999
Mesifos studie (Wunderink, 2006)	**1,55** at risk functionele psychosen		25,7 jaar (SD 6,6)		29,0 jaar (SD 8,1)	3:1	Pop van 1.333.000 at risk n=206	18-45	SCAN DSM-IV	2002
Huidige studie (Boonstra, 2007)	**2,2** at risk niet affectieve psychosen	**2,7** at risk niet affectieve psychosen	27,1 jaar (SD 6,0)	**1,6** at risk niet affectieve psychosen	29,6 jaar (SD 8,7)	1,8:1	Pop van 404.909 at risk n=75	18-45	DSM-IV	2002

RESULTATEN

Het totale aantal inwoners in de leeftijdscategorie 18-45 jaar, de risicopopulatie, bedroeg 404.909 inwoners, van wie 210.294 (51,9%) mannen. 6477 personen in deze leeftijdscategorie werden in 2002 verwezen naar een van beide GGZ instellingen. De dossiers van 892 patiënten konden om verschillende redenen niet worden gescreend. Van 526 patiënten bevatte het dossier geen bruikbare informatie en van 366 patiënten was het dossier onvindbaar. De 5585 overblijvende dossiers (86.2%) waren geschikt voor verder onderzoek. In 242 dossiers (4,3%) werd één of meer van de specifieke psychotische symptomen gerapporteerd. Het betreft 140 (58%) mannen en 102 (42%) vrouwen. In 182 dossiers werden wanen gerapporteerd, in 90 dossiers hallucinaties, in 37 dossiers chaotisch of katatoon gedrag en in 17 dossiers onsamenhangende spraak.

Tabel 2. Verdeling psychotische symptomen per diagnostische groep volgens classificatie na 6 maanden

	N	NAPS	APS	Anders	Geen
1 sx	167	45 (27 %)	12 (7 %)	61 (37 %)	49 (29 %)
2 sx	66	40 (61 %)	3 (5 %)	15 (23 %)	8 (12 %)
3 sx	8	4 (50 %)	2 (25%)	1 (12.5%)	1 (12.5%)
4 sx	1	1 (100%)	0	0	0
Totaal	242	90 (37 %)	17 (7 %)	77 (32 %)	58 (24 %)

NAPS = niet affectieve psychotische stoornis
APS = affectieve psychotische stoornis
Anders = andere diagnostische groepen
Geen = geen diagnose
Sx = symptoom zoals beschreven onder paragraaf A in de sectie “schizofrenie en andere psychotische stoornissen” in de DSM-IV

Bij 90 patiënten werd gedurende de eerste zes maanden na het eerste contact een klinische diagnose gesteld van een niet-affectieve psychotische stoornis. In tabel 2 wordt een overzicht gegeven van het aantal symptomen en de klinische diagnosen van de onderzoekspopulatie. Van de 90 patiënten met een niet-affectieve psychotische stoornis, was de diagnose bij 75 patiënten na 30 maanden follow-up nog altijd een niet-affectieve psychotische stoornis. Deze 75 patiënten worden gerekend tot de geregistreerde of administratieve incidentie. Aangezien 86% van de dossiers zijn onderzocht, wordt bij de berekening van de incidentie overeenkomstig gedeeld door 86% van het totale inwoneraantal. Dit levert een administratieve incidentie op van 2,2 (95% BI 1,7-2,6) per 10.000 inwoners at risk.

Van de 75 patiënten waren er 49 (65%) man. Dit betekent een incidentie voor mannen van 2,7 (95% BI 2,1-3,4) en voor vrouwen van 1,6 (95% BI 1,0-2,1) per 10.000 inwoners at risk. De administratieve incidentie van niet-affectieve psychotische stoornissen voor mannen is dus bijna twee keer zo hoog als voor vrouwen. 24 patiënten met een begindiagnose van een niet-affectieve psychotische stoornis (inclusief schizofrenie) behielden of kregen na dertig maanden follow-up de diagnose schizofrenie wat neerkomt op een administratieve incidentie van 0,7 (95% BI 0,4-1,0) per 10.000 inwoners at risk. Naast de 15 patiënten met een begin diagnose van een niet affectieve psychotische stoornis welke na 30 maanden follow-up niet gehandhaafd werd, kregen 16 patiënten een andere begindiagnose maar werd na 30 maanden follow-up een niet affectieve psychotische stoornis gediagnosticeerd. Deze patiënten zijn niet meegenomen in de incidentieberekening. Als dit wel zou zijn gedaan ligt de incidentie een stuk hoger.

Het eerste zorgcontact met de GGZ in verband met een niet affectieve psychotische stoornis was bij mannen op jongere leeftijd dan bij vrouwen. De gemiddelde leeftijd voor mannen van 27,1 jaar (SD = 6,0) was significant lager ($p<0,003$) dan voor vrouwen (29,6 jaar, SD = 8,7). Beide regio's verschilden niet significant van elkaar ($p>0,2$). De incidentie in het verzorgingsgebied van GGZ Friesland was 2,0/10.000 inwoners at risk (95%BI 1,5-2,5) en van Mediant Twente 2,4/ 10.000 inwoners at risk (95% BI 1,7-3,1).

CONCLUSIE EN DISCUSSIE

De belangrijkste bevindingen van deze studie zijn dat de administratieve incidentie van beide regio's overeen komt met de gevonden incidentie in de Nederlandse studies van Giel (1980) en Wunderink (2006), lager ligt dan de bij uitstek verstedelijkte Haagse regio met de verwachte scheve geslachtsverdeling (M>V) (Selten, 2001) en geen grote verschillen laat zien tussen het overwegend rurale Friesland en het meer urbane Twente.

INCIDENTIE

In vergelijking met de incidentiecijfers uit de review van McGrath zit de in deze studie gevonden incidentie van niet-affectieve psychotische stoornissen van 2,2/10.000 in het 75ste percentiel van die studie. Dat betekent dat 75% van de in de review geincludeerde patiënten, in een studie zaten met een incidentie lager dan 2,2/10.000 inwoners.

De gevonden administratieve incidentie komt overeen met de gemiddelde incidentie van de Nederlandse studies in de afgelopen 30 jaar. De incidentie van niet-affectieve psychosen van 2,2/10.000 inwoners van 18-45 jaar is naast de overeenkomst met andere Nederlandse studies ook vanwege de gebruikte onderzoeksmethode en de langdurig stabiele klinische diagnose een relatief betrouwbaar gegeven. Het be-

trof een op gangbare wijze gestelde klinische diagnose, en geen gestandaardiseerde diagnostiek met behulp van een gevalideerd diagnostisch instrument. De methode van onderbouwing van de klinische diagnose met een of meer gerapporteerde symptomen is in analogie met de OPCRIT methode verantwoord om van klinische diagnose tot research diagnose te komen (McGuffin, 1991, Vares, 2006). Hoewel de gevolgde procedure in dit onderzoek verschilt van die van elders, hetgeen een zekere beperking met zich meebrengt, maakt de kwaliteit van het diagnostische proces, de verslaglegging daarover, de zorgvuldigheid waarmee tot een klinische diagnose is gekomen, en de langdurige stabiliteit van de diagnose (follow-up van 30 maanden), een vergelijking met de andere studies wetenschappelijk verantwoord. De betrouwbaarheid van deze procedure is bovendien voldoende gebleken. Daarbij is eerder sprake van onderschatting dan overschatting van de incidentie, alleen al vanwege het niet meerekenen van patiënten met een andere begindiagnose en van patiënten met een begin diagnose van een niet affectieve psychotische stoornis welke niet na 30 maanden gehandhaafd bleef. Zouden die allen alsnog tot de doelgroep worden gerekend dan wordt de incidentie 3/10.000 inwoners. Daarnaast kunnen onderdetectie van psychotische symptomen, leeftijdsgrens van 18-45 jaar en mogelijk onvoldoende valide diagnostiek bijdragen aan een onderschatting van de werkelijke incidentie.

Zowel de diagnose als symptoombepaling zijn gebaseerd op rapportage in het dossier en daarmee volledig gebaseerd op de klinische blik van de hulpverlener. Systematische screening op psychotische symptomen, systematische diagnostiek van patiënten met psychotische symptomen en monitoring van patiënten met een psychotische stoornis zou dan ook alleszins gerechtvaardigd zijn.

GESLACHTSVERDELING

Tot voor kort was de dominante opvatting dat de incidentie voor mannen gelijk was aan de incidentie voor vrouwen. In meer recente studies wordt aangetoond dat mannen een hoger risico hebben op een niet-affectieve psychotische stoornis. In de meta-analyse van Aleman werd aangetoond dat er verschil is tussen man en vrouw in het risico op schizofrenie in de verhouding van 1,42:1 (95% BI 1,30-1,56) (Aleman, 2003). Deze zelfde geslachtsverdeling van 1,4:1 vindt McGrath (2004) ook. De geslachtsverschillen waren significant lager in studies met geboortejaren van voor 1980 dan in studies met steekproeven uit geboortejaren na 1980. Het grotere risico voor mannen kon niet worden verklaard door de invloed van leeftijdsgrenzen of diagnostische criteria. De man-vrouw verhouding in onze onderzoekspopulatie wordt schever naar mate de diagnostische criteria strenger worden. In de patiëntenpopulatie met gerapporteerde psychotische symptomen was de man-vrouw verhouding 1,4 ($p>0,06$), in de groep patiënten met een diagnose van niet-affectieve psychotische stoornis 1,7 ($p<0,03$) en onder de patiënten met de diagnose schizofrenie 3 ($p<0,04$).

LEEFTIJD WAAROP DE PSYCHOSE BEGINT

De leeftijd waarop de eerste psychose zich voordoet is bij vrouwen over het algemeen hoger dan bij mannen (Häfner, 1998, Aleman, 2003). Gemiddeld zijn vrouwen ongeveer 3 à 4 jaar ouder dan mannen. In deze studie werd een leeftijdsverschil van 2,5 jaar gevonden. De gemiddelde leeftijd van 27,1 jaar voor mannen en 29,6 jaar voor vrouwen met een niet-affectieve psychotische stoornis komt redelijk overeen met die in de recentere incidentiestudies in Nederland.

VERSCHILLEN PER GEBIED

De incidenties tussen beide regio's verschilden niet significant van elkaar ($p>0,2$), al is er wel sprake van een hogere incidentie in het meer verstedelijkte Twente. Dit verhoogt de betrouwbaarheid van de gevonden incidentie voor rurale gebieden, de gegevens zijn mogelijk niet representatief voor sterk stedelijke gebieden, zoals rond de grote steden.

LITERATUURLIJST

Aleman, A., Kahn, R.S., Selten, J.P. (2003). Sex differences in the risk for schizophrenia, evidence from meta-analysis, Archives of General Psychiatry, 60:565-571.

American Psychiatric Association Diagnostic and statistical manual of mental disorder, DSM-IV, 1994.

Brown, L. D., Cai, T. T., and DasGupta, A. Interval Estimation for a Binomial Proportion. Statistical Science 16(2): 101-117, 2001.

Crow T.J. (2000). Schizophrenia as the price that homo sapiens pays for language: a resolution of the central paradox in the origin of the species. Brain Research Brain Research Reviews, 31:118-129.

Giel, R., Sauer, H. C., Slooff, C. J. (1980). Over de epidemiologie van functionele psychosen en invaliditeit. Tijdschrift voor psychiatrie, 22: 11-12.

Häfner, H.(1998). Onset and course of first schizophrenic episode, The Kaohsiung. journal of medical sciences., 7:413-431.

Jablensky A, Sartorius N, Ernberg G, e.a. (1992). Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. Psychological Medicine Monograph Supplement, 20:1-97.

McGrath J, Saha S, Welham J, e.a. (2004). A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Medicine, 2:13.

McGuffin P, Farmer A, Harvey I. (1991) A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. Arch Gen Psychiatry 48(8):764-70.

Selten JP, Veen N, Feller W, e.a. (2001).: Incidence of psychotic disorders in immigrant groups to The Netherlands. British Journal of Psychiatry, 178:367-372.

Vares M, Ekholm A, Sedvall GC, Hall H, Jonsson EG. (2006) Characterization of patients with schizophrenia and related psychoses: evaluation of different diagnostic procedures. Psychopathology 39(6):286-95.

Wunderink A, Nienhuis FJ, Sytema S, e.a. (2006). Treatment delay and response rate in first episode psychosis. Acta Psychiatrica Scandinavica, 113:332-339.

SUMMARY

BACKGROUND

Research on risk factors for schizophrenia renewed the attention for geographical differences in the incidence and gender distribution of schizophrenia. The registered incidence by mental health care services of non-affective psychotic disorders in the Netherlands is unknown.

AIM OF THE STUDY

Determine the mental health care registered incidence in 2002 of non-affective psychotic disorders in Friesland and Twente.

METHOD

The medical files of all first contact patients with mental health services in 2002 (n=6477) in two mental health care services were screened on psychotic symptoms. All patients with psychotic symptoms (N=242) were included and their clinical diagnosis recorded, After 30 months of follow-up the most recent clinical diagnosis was recorded again.

RESULTS

Within six months after first contact 75 patients were diagnosed with non-affective psychotic disorder, which diagnosis was maintained at follow-up after 30 months, an incidence of 2.2/10.000 inhabitants. The male-female ratio was 1.8:1. The incidence of non-affective psychotic disorder did not differ significantly between the two regions.

CONCLUSION

The incidence found corresponds with the incidence found in earlier Dutch studies and lays on the 75th percentile of the cumulative incidence found in an international review.

Keywords: incidence, detection, first episode psychosis, non-affective psychotic disorder, schizophrenia.

CHAPTER 3

Detection of psychosis by mental health care services; a naturalistic cohort study

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ABSTRACT

BACKGROUND

Detection of psychotic disorders is an important issue, since early treatment might improve prognosis. Timely diagnosis of psychotic disorders depends on recognition of psychotic symptoms and their interpretation. The aim of this study is to examine to what extent reported psychotic symptoms are accounted for in clinical diagnosis.

METHODS

The medical files of all patients who had a first contact with one of two mental health care services (N = 6477) were screened for reported psychotic symptoms and subsequent clinical diagnosis. Patients who reported psychotic symptoms and who were diagnosed with a psychotic disorder were followed-up for two years to register prescription of antipsychotic treatment and continuity of care.

RESULTS

In the files of 242 (3.7%) patients specific psychotic symptoms were recorded. 37% of these patients were diagnosed with a non-affective psychotic disorder, 7% with other psychotic disorders and 56% with non-psychotic disorders or no diagnosis at all. About 90% of the patients diagnosed with a psychotic disorder did receive any prescription of antipsychotics, and about 50% were in continuous care during the first 2 years.

CONCLUSIONS

Relatively large proportions of patients presenting with psychotic symptoms were diagnosed with a non-psychotic diagnosis or not diagnosed at all. This applies also to patients reporting at least two or more psychotic symptoms. Although we did not verify the appropriateness of clinical diagnosis, these findings are an indication that psychotic disorders may be underdetected. Improving the diagnostic process in mental health care services may be the most obvious way to promote early intervention in psychosis.

Keywords; non-affective psychotic disorder, schizophrenia, guideline, diagnosis, antipsychotics

BACKGROUND

Early detection and intervention of psychotic disorders are important issues in mental health practice and research (2;3). Different strategies have been developed to improve the detection of first episode psychosis both in the prodromal phase and during the first psychotic episode to minimize the delay of treatment after the onset of psychosis (4;5). The role of treatment delay has been shown to be an important factor associated with response to antipsychotic treatment, in terms of severity of global psychopathology, positive and negative symptoms, functional outcomes and time to response (6-8). As a consequence, it was hypothesized that reducing the duration of untreated psychosis would improve outcome (9-14). Therefore it is essential that patients who report psychotic symptoms at first contact with mental health services are adequately diagnosed and treated accordingly. The APA practice guidelines for the treatment of patients with schizophrenia (15;16) as well as the Dutch guidelines (17) provide recommendations for treatment in every phase of the illness. The most important interventions for first episode psychosis are: accurate diagnostic assessment, initiating antipsychotic medication as soon as it is feasible, and continuation of antipsychotic treatment after response for at least one year in the APA guidelines and at least two years in the Dutch guidelines. The recommended duration of antipsychotic prophylaxis in the Dutch guidelines is one year longer, because relapse rates do not seem to level off during the first years after remission from a first episode (18).

Despite the importance of treatment guidelines, however, implementation has been shown to be difficult to achieve (19-21). The aim of the study is to examine to what extent reported psychotic symptoms are accounted for in clinical diagnosis and subsequent treatment.

METHODS

STUDY DESIGN

The design of the study is an administrative inquiry into the diagnostic and daily practice of mental health care services regarding patients who report psychotic symptoms at first contact. The study was conducted in two mental health regions of The Netherlands, with 1.028 million inhabitants on January 1, 2002. The two regions were Friesland (636,000 inhabitants) and Twente (392,000 inhabitants). The total number of inhabitants between 18-45 years of age, representing the at risk population, was 404,909, of which 210,294 (51.9%) were males.

The medical records of all patients between 18-45 years of age who had a first contact with mental health care services in 2002 were screened for reported specific psychotic symptoms and their initial clinical DSM-IV diagnosis. All available documents from the first six months after first contact were taken into account. Patients

with at least one of four specific psychotic symptoms were included and followed-up for two years. The psychotic symptoms screened for were the symptoms listed under paragraph A in the schizophrenia section of the DSM-IV: delusions, hallucinations, disorganized speech and grossly disorganized behaviour (1). After thirty months of follow-up medical files were screened retrospectively for final DSM-IV diagnosis, any prescription of antipsychotic treatment and continuity of care during two year follow-up.

RESULTS

Of 404,909 inhabitants between 18-45 years of age, 6477 (1.6%) were referred to mental health services for a first ever contact in 2002. The medical files of 892 patients were excluded (14%) due to lack of information (526) or availability (366). 5585 medical files were eligible for further research. In the files of 242 patients one or more specific psychotic symptoms were reported; 140 patients (58%) were males. In 182 files delusions were reported, in 90 files hallucinations, in 37 files grossly disorganized behaviour and in 17 files disorganized speech.

As shown in table 1, at baseline 90 patients (37%) were diagnosed according to DSM-IV with a non-affective psychotic disorder (NAPD): schizophrenia, schizophreniform disorder, brief psychotic disorder, schizoaffective disorder, delusional disorder or psychotic disorder not otherwise specified. 17 patients (7%) were diagnosed with other psychotic disorders: organic or substance induced psychotic disorder (n=6), affective episode with psychotic features (n= 6) or schizophrenia spectrum personality disorder (5). The other 135 patients were diagnosed with non-psychotic disorders (n=77, 32%) or were not diagnosed at all (n=58, 24%). 75 patients (31%) who reported psychotic symptoms had a combination of two or more psychotic symptoms, of whom 45 were diagnosed with a non-affective psychotic disorder (NAPD) and the other 30 patients with other psychotic disorders or a non-psychotic disorder. 16 patients (53%) were diagnosed as a non-affective psychotic disorder sometime during the follow-up period. A combination of at least three symptoms was reported in the records of 9 patients. Of the 167 patients with one reported psychotic symptom, 45 (27%) were diagnosed with a non-affective psychotic disorder.

Table 1. Psychotic symptoms per diagnostic group

	NAPD	OPD	Other	None	N
1 sx	45 (27 %)	12 (7 %)	61 (37 %)	49 (29 %)	167 (100%)
2 sx	40 (61 %)	3 (5 %)	15 (23 %)	8 (12 %)	66 (100%)
3 sx	4 (50 %)	2 (25%)	1 (12.5%)	1 (12.5%)	8 (100%)
4 sx	1 (100%)	0	0	0	1 (100%)

NAPD = non-affective psychotic disorder **OPD** = other psychotic disorders
Other = other disorders **Sx** = symptoms

Table 2. Treatment per diagnostic group

	Prescription of antipsychotics	Continuous care	N
NAPD	81 (90%)	46 (51%)	90 (100%)
OPD	15 (88%)	6 (35%)	17 (100%)
Other	33 (43%)	27 (35%)	77 (100%)
None	29 (50%)	14 (24%)	58 (100%)

NAPD = non effective psychotic disorder **OPD** = other psychotic disorders **Other** = other disorders

As shown in table 2, antipsychotic medication has been prescribed anytime during the follow-up period to 158 patients (65%). Of the 90 patients with a non-affective psychotic disorder antipsychotics were prescribed to 81 patients (90%). Of the patients diagnosed with other psychotic disorders (n=17), 88% received a prescription of antipsychotic medication. Patients diagnosed with other disorders or without any specified diagnosis received a prescription of antipsychotic medication in 46%. Of the 90 NAPD patients, 46 (51%) received continuous care for at least two years.

DISCUSSION

The present study, in which more than 5500 medical files were studied from the population of two mental health regions, revealed that many patients presenting psychotic symptoms are not adequately diagnosed. Even when two psychotic symptoms are presented, 25% of patients received a non-psychotic diagnosis or no diagnosis at all. In case one psychotic symptom was stated in the files, the chance of getting a psychotic diagnosis is only 33%. These data strongly indicate that psychosis in mental health care is under detected. We were not able to estimate the prevalence of underdetection of psychosis because of a number of limitations of the study. We were not able to verify clinical diagnosis by a standardized diagnostic procedure, and therefore some of the clinically assigned diagnoses might indeed be appropriate (e.g. in case of PTSS or personality disorder with psychotic symptoms). This study completely relied on reported psychotic symptoms as written in the medical files. Such symptoms might not have been recorded or even noticed and therefore have escaped proper attention. Underdetection of psychotic symptoms may also contribute to underdetection of NAPD. Systematic examination of psychotic experiences at first contact with mental health services may serve as a useful measure to overcome this limitation of our study and of clinical practice. The results did not differ between the two regions with only two mental health care services which were both included in the study, so it is unlikely that local factors played an important role or that patients received treatment elsewhere.

90% of the patients clinically diagnosed with a non-affective psychotic disorder

received at least one prescription of antipsychotic medication while half of them received continuous care for at least two years. We may conclude that if clinical diagnosis of a non-affective psychotic disorder has been established, proper treatment consequences are more or less assured. This underlines the importance of timely detection of psychotic disorder by mental health care services. Effort should be primarily directed to patients referred to mental health care services in stead of to individuals who do not yet seek help.

LIST OF ABBREVIATIONS

COMPETING INTERESTS

There is no competing interest for any of the authors.

AUTHORS' CONTRIBUTIONS

NB conceived the study, carried out the field study, performed the statistical analysis and drafted the manuscript. LW participated in the design of the study and helped to draft the manuscript. SS supported the statistical analysis and revised the manuscript. DW contributed to the study design and revised the manuscript. All authors read and approved final manuscript.

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REFERENCE LIST

(1) Hanssen M, Peeters F, Krabbendam L, Radstake S, Verdoux H, van Os J. How psychotic are individuals with non-psychotic disorders? Soc Psychiatry Psychiatr Epidemiol 2003; 38(3):149-154.

(2) Lambert M, Conus P, Schimmelmann BG, Eide P, Ward J, Yuen H et al. Comparison of olanzapine and risperidone in 367 first-episode patients with non-affective or affective psychosis: results of an open retrospective medical record study. Pharmacopsychiatry 2005; 38(5):206-213.

(3) Harrigan SM, McGorry PD, Krstev H. Does treatment delay in first-episode psychosis really matter? Psychol Med 2003; 33(1):97-110.

(4) Lieberman JA, Fenton WS. Delayed detection of psychosis: causes, consequences, and effect on public health. Am J Psychiatry 2000; 157(11):1727-1730.

(5) Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry 2005; 162(10):1785-1804.

(6) Wunderink A, Nienhuis FJ, Sytema S, Wiersma D. Treatment delay and response rate in first episode psychosis. Acta Psychiatr Scand 2006; 113(4):332-339.

(7) Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. Arch Gen Psychiatry 2005; 62(9):975-983.

(8) Ho BC, Andreasen NC, Flaum M, Nopoulos P, Miller D. Untreated initial psychosis: its relation to quality of life and symptom remission in first-episode schizophrenia. Am J Psychiatry 2000; 157(5):808-815.

(9) Larsen TK, McGlashan TH, Johannessen JO, Friis S, Guldberg C, Haahr U et al. Shortened duration of untreated first episode of psychosis: changes in patient characteristics at treatment. Am J Psychiatry 2001; 158(11):1917-1919.

(10) Loebel AD, Lieberman JA, Alvir JM, Mayerhoff DI, Geisler SH, Szymanski SR. Duration of psychosis and outcome in first-episode schizophrenia. Am J Psychiatry 1992; 149(9):1183-1188.

(11) McGorry P, Nordentoft M, Simonsen E. Introduction to “Early psychosis: a bridge to the future”. Br J Psychiatry Suppl 2005; 48:s1-s3.

(12) Melle I, Haahr U, Friis S, Hustoft K, Johannessen JO, Larsen TK et al. Reducing

the duration of untreated first-episode psychosis -- effects on baseline social functioning and quality of life. Acta Psychiatr Scand 2005; 112(6):469-473.

(13) Norman RM, Malla AK. Duration of untreated psychosis: a critical examination of the concept and its importance. Psychol Med 2001; 31(3):381-400.

(14) Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association. Am J Psychiatry 1997; 154(4 Suppl):1-63.

(15) APA Practice guidelines workgroup on schizophrenia. Practice guideline for the treatment of patients with schizophrenia second edition 2004.

(16) Schizofrenie Stichting Nederland. Consensus document Schizofrenie Stichting. 1996.

(17) Bosveld-van Haandel LJ, Slooff CJ, van den Bosch RJ. Reasoning about the optimal duration of prophylactic antipsychotic medication in schizophrenia: evidence and arguments. Acta Psychiatr Scand 2001; 103(5):335-346.

(18) Davis DA, Taylor-Vaisey A. Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. CMAJ 1997; 157(4):408-416.

(19) Gaebel W, Weinmann S, Sartorius N, Rutz W, McIntyre JS. Schizophrenia practice guidelines: international survey and comparison. Br J Psychiatry 2005; 187:248-255.

(20) Milner KK, Valenstein M. A comparison of guidelines for the treatment of schizophrenia. Psychiatr Serv 2002; 53(7):888-890.

(21) American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV, 1994.

CHAPTER 4

Duration of untreated psychosis and negative symptoms - a systematic review and meta-analysis of individual patient data

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ABSTRACT

BACKGROUND

Longer duration of untreated psychosis (DUP) is associated with poorer outcome in terms of positive symptoms, relapse rate, and time to remission. In contrast, the association with negative symptoms is less consistent.

AIMS

The study had three aims. First, to arrive at a more precise estimate of the correlation between DUP and negative symptoms than previous reviews, by substantially increasing the amount of available data. Second, to see whether the strength of this correlation attenuated over longer follow-up intervals. Third, to determine whether there is a relationship between DUP and changes in negative symptoms.

METHOD

Relevant databases were searched for studies published between December 1992 and March 2009 that reported data on DUP and negative symptoms. We obtained individual patient data where possible and calculated summary correlations between DUP and negative symptoms for each study at baseline, short and long-term follow-up. We used multilevel regression analysis to examine whether the effect of DUP on negative symptoms was greatest in the early stages of illness.

RESULTS

We included 28 non-overlapping studies from the 402 papers detected by the search strategy. After contacting the authors we obtained individual patient data from 16 of these studies involving 3339 participants. The mean DUP was 61.4 weeks (SD= 132.7, median DUP= 12.0). Shorter DUP was significantly associated with less severe negative symptoms at baseline and also at short (1-2 year) and longer term follow-up (5-8 year) ($r=0.117$, 0.180 and 0.202 respectively, $p<.001$).The relationship between improvement in negative symptoms and DUP was found to be non-linear, for example: people with a DUP shorter than 9 months showed substantially greater negative symptom reduction than those with a DUP of greater than 9 months.

CONCLUSIONS

Shorter DUP is associated with less severe negative symptoms at short and long-term follow up, especially when the DUP is less than 9 months. Since there is no effective treatment for negative symptoms, reducing DUP to under 9 months may be the best way to ameliorate them.

KEYWORDS

First episode psychosis, schizophrenia, treatment delay, negative symptoms.

INTRODUCTION

Negative symptoms are a core component of the schizophrenia syndrome and are commonly described in terms of five dimensions: blunted affect, alogia, anhedonia, avolition and asociality (1-3). Negative symptoms are associated with poor functional outcome (4), cognitive deficits (5), social dysfunction and poor quality of life (6-8). Negative symptoms are common: the prevalence in short-term follow-up studies (up to 2.5 years) is about 45% (4;9;10), and in longer term studies (7.5-10 years) 20-30% (11).

There is no established treatment for primary negative symptoms (2;12). Pharmacological treatments, such as neuroleptics have only a marginal impact on negative symptom severity (13). Psychosocial treatments for negative symptoms have no substantial evidence base in their favor, although there have been three small but promising trials (peer support groups (14), music therapy (15) and body oriented psychosocial therapy (16)).

Pending replication of these studies, it may be that the best way to deal with negative symptoms is prevention. Many countries have already adopted an early intervention approach to the treatment of psychosis on the basis that there is a proven association between duration of untreated psychosis and the long-term severity of positive symptoms. A similar association between negative symptoms and outcome would support early intervention for negative symptoms (17).

So far two meta-analyses have examined the correlation between DUP and negative symptoms (18;19). The first, by Marshall et al. reported an association at 6 and 12 months but not at baseline and 24 months (18). The second, by Perkins et al. claimed that patients with shorter DUP experienced less negative symptoms baseline and at follow-up (19). Whilst making a valuable contribution, both reviews share three limitations. First, neither study provided a precise analysis of the effect of DUP at long term follow-up, thus: Marshall et al, did not consider data on negative symptoms beyond 24 months and Perkins et al. summarized data of all follow-up assessments varying from 3 months to 15 years into one combined effect size. Second, both studies relied exclusively on published data, which meant that they excluded a substantial number of studies that collected pertinent data but did not publish it in a format that could be used in their analyses. Third, both studies used combined correlation coefficients calculated by different techniques, for example parametric in some studies and non-parametric in others.

As a consequence of these limitations, neither study was able to consider the nature of the relationship between DUP and negative symptoms. It is now well established that there is a non-linear relationship between DUP and positive symptoms (20). This means that in a patient with a DUP of less than 12 months, the effect of a DUP

reduction of for example 2 months on positive symptoms would be greater than a two month reduction in someone with a DUP of more than 12 months. It is possible therefore that a similar non-linear relationship might exist with negative symptoms, with important clinical implications.

The present study therefore had three aims: (a) to provide a precise estimate of the correlation between DUP and negative symptoms by substantially increasing the amount of available data contributing to the analysis; (b) to see if the strength of any correlation attenuates at longer follow up intervals; (c) to determine whether the relationship between DUP and negative symptoms was non-linear.

METHODS

To overcome the limitations of previous meta-analyses it was necessary to obtain a substantial dataset of individual patient data (IPD) from first-episode studies. The use of individual patient data is the gold standard for meta-analysis (21;22) and offers a greater resolution of effect size than meta-analyses based on study level data. Individual patient data permitted us to reanalyze all the data using the same method of correlation and to calculate correlations that had not been previously published. We were also able to combine data across studies to explore the relationship between DUP and negative symptoms.

SEARCH STRATEGY

The search aimed to detect all studies that had examined DUP and negative symptoms in first episode psychotic patients, and which were available for review up to March 2009. The search included the databases MEDLINE and PUBMED using the keywords “DUP” AND “psychosis” OR “schizophrenia” and the combination “duration” AND “untreated” AND “psychosis” OR “schizophrenia”. In addition references cited in these papers were examined.

INCLUSION CRITERIA AND DATA EXTRACTION

Studies were included if they met two criteria. First, participants had experienced a first episode of psychosis defined as: schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder or psychosis NOS, according to either the Diagnostic Statistical Manual (DSM-IV) or the International Classification of Diseases (ICD-10) classification systems. Second, DUP and negative symptoms had been measured using a standardized method (which for negative symptoms was one of the three commonly used scales in this area, i.e.: the Positive and Negative Symptom Scale (PANSS) (23), the Scale for the Assessment of Negative Symptoms (SANS) (24), or the Brief Psychiatric Rating Scale (BPRS) (25)).

Abstracts were screened independently by two reviewers (N.B. and R.K.), and co-

pies were obtained of any papers describing potentially eligible studies. Each paper was assessed independently by two reviewers and any disagreements resolved by discussion with a third reviewer (L.W.) (for table of included studies see Appendix 1). The authors of included studies were contacted and asked to provide anonymized individual patient data on: gender, age at onset, DUP, and negative symptom scores at baseline and all available follow-up points.

ANALYSIS

We calculated the correlation between DUP and negative symptoms for short and long term follow up. We defined short-term follow up as between 12 to 24 months and long term follow up as 60 to 96 months. Studies of which a spearman correlation was published were used for sensitivity analysis.

In cases where more than one assessment was available for short or long term follow up, we used the first assessment. The data were analyzed using a two-step approach. First, individual patient data from each study were analyzed using the non-parametric Spearman's Rank Correlation. We choose a non-parametric test because of the significant positive skew in the distribution of DUP. In the second step, a meta-analysis of the aggregated data produced for each study was performed using Comprehensive Meta- Analysis in order to summarize the correlations (CMA, version 2005, Biostat, Inc, Englewood, NJ, 2005) (26). We used random effect models because of great differences between research designs. Correlation data were synthesized with Fisher's z transformation into a single correlation coefficient (r) with 95% confidence intervals (CI).

CMA also tests for the heterogeneity of the sample populations using I^2, a test parameter, which evaluates the null hypothesis that all studies are assessing the same effect size. I^2 indicates the percentage of total variation across studies due to heterogeneity rather than chance, and ranges from 0% (no heterogeneity) to 100% (high heterogeneity). Values for I^2 of 25%, 50% and 75% are considered to represent low, moderate and high heterogeneity respectively (27).

A major concern when conducting a meta-analysis is publication bias: studies that report relatively large effect sizes are more likely to be published than studies with smaller effect sizes. If the included studies are a biased sample of all relevant studies, consequently the bias will be reflected in the mean effect computed by the meta-analysis. A funnel plot can be made to examine the publication bias using Comprehensive Meta-Analysis (CMA, version 2005, Biostat, Inc, Englewood, NJ, 2005).

We examined the nature of the relationship between DUP and negative symptom change using the method developed by Drake (20). We used a multilevel regression analysis (XTREG in STATA release 11.0) (28;29) to estimate the magnitude of the effect of DUP on negative symptom severity reduction after various periods of follow-

up with the individuals nested within each study. Subsequently, explanatory variables (gender and age at onset) were added, as potential confounders. The skewed distribution of DUP was corrected by converting DUP to its logarithm (logDUP) thus allowing the use of parametric statistics. The change of negative symptoms from baseline to follow-up was calculated as a percentage of baseline negative symptom severity and added in the multilevel regression analysis as the dependent variable. We conducted the analysis for negative symptom change at short and long-term follow up, as defined above.

RESULTS

STUDIES AND PATIENTS

A total of 402 papers were identified by the search strategy, from which we identified 28 non-overlapping first episode studies that met inclusion criteria (see Appendix 1) (20; 30-56). The selected studies included a total of 3998 participants. Following written requests, authors of 16 studies submitted their data sets which covered a total of 3339 participants. From the 12 studies of which individual patient data was not available, 2 studies reported a spearman correlation at short term follow-up (1-2 years). Table 1 shows the distribution of DUP, gender and age at onset of participants for whom individual patient data were available at baseline. The follow-up data of 2 studies were incomplete and therefore only baseline data were used in our analysis (43;47).

The mean age at onset of participants was 26.0 years (SD=8.9), and the mean DUP was 61.4 weeks (SD= 132.7 weeks, median DUP= 12.0 weeks). 59% of the participants at baseline were males. Mean age at onset for males was 25.0 years (SD=8.6) and for females 27.3 years (SD=9.2). There was no statistically significant difference in DUP between male and female participants (61.0 weeks and 61.9 weeks respectively.

Appendix 1. Description of included cohorts

Cohort	Cohort size	Country	Age of population in years	Length of follow up (months)	Symptom scale
Addington, 2004 (22)	240	Canada	-	36	PANSS
Barnes, 2000 (23;24)	98	United Kingdom	16-55	12	SANS
Black, 2001 (25)	21	Canada	-	6	PANSS
Chen, 2005(26)	93	Hong Kong	18-55	36	PANSS
Clarke, 2006 (27)	152	Ireland	12>	96	PANSS
Craig, 2000 (28)	354	United States	15-60	24	SANS
Crespo-Faccoro, 2007 (29)	61	Spain	15-60	36	SANS
Cullberg 2002 (30;31)	175	Sweden	18-45	60	BPRS
De Haan, 2003 (32;33)	88	The Netherlands	Adolescents	72	PANSS
Drake (34)	255	United Kingdom	16-64	18	PANSS
Gorna, 2008 (35)	86	Poland	Adults	60	PANSS
Harris, 2005 (36)	318	Australia	16-45	96	SANS
Ho, 2000 (37)	74	United States	-	6	SANS
Larsen, 2000(38)	43	Norway	15-55	12	PANSS
Malla, 2007 (39)	172	Canada	16-50	12	PANSS
Malla, 2003 (40)	15	Canada	16-50	36	SANS,
Manchanda, 2005(41)	122	Canada	16-50	24	SANS
Melle, 2004 (42)	301	Scandinavia	18-65	24	PANSS
Montague (43)	109	United Kingdom	16-50	120	SANS
Oosthuizen, 2005(44)	57	South Africa	16-55	24	PANSS
Petersen, 2005 (45)	578	Scandinavia	18-45	24	SANS
Sim, 2004(46;47)	278	Singapore	18-40	24	PANSS
Ucok, 2006 (48)	148	Turkey	15-45	12	SANS
Verdoux, 2001 (49)	65	France	< 60	24	PANSS
Vyas, 2007 (50)	40	United Kingdom	Adolescents	48	PANSS
Wade, 2005 (51)	126	Australia	15-30	15	SANS
Wunderink, 2006 (52)	157	The Netherlands	18-45	24	PANSS
Yamazawa, 2008(53)	34	Japan	16-44	12	PANSS

DUP definition	DUP measure
From the time the individual first described the onset of any positive sx that could be rated as 4 or more on the PANSS until the first effective treatment was initiated.	IRAOS
Onset of psychotic sx to first treatment with antipsychotic medication.	NS
Onset of positive psychotic sx (score of ≥4 on any of the positive subscale items in the PANSS, these sx must have lasted throughout the day for several days or appeared several times a week) until the beginning of treatment with antipsychotic medication.	IRAOS
Onset date for the earliest psychotic sx.	IRAOS.
First noted psychotic symptoms to presentation to the psychiatric services for initiation of adequate treatment of a psychotic illness.	SCID
Occurrence of the first clear psychotic symptom to first psychiatric hospitalization.	SCID
First continuous (present most of the time) psychotic symptoms to initiation of adequate antipsychotic drug treatment.	SCID
First psychotic sx until the first contact with psychiatric services.	SCID
First onset of psychotic sx until start of antipsychotic medication (for a minimum of 6 weeks).	NS
Onset of delusions and hallucinations.	NS
Onset of first psychotic symptoms to the initiation of antipsychotic treatment	ICD 10
Onset of psychosis to initiation of treatment.	RPMIP
Onset of first sx to the initiation of neuroleptic treatment	CASH + PSYCH-base
Onset of psychotic sx to hospitalization for psychosis or initiation of adequate treatment.	SCID
Onset of psychotic sx to the time of initiation of continuous antipsychotic treatment, plus any periods of psychosis previously experienced and spontaneously remitted.	CORS
Initial onset of psychosis to treatment (antipsychotic medication of a dosage that should actually lead to a significant response in most patients for a period of time (4 weeks)).	SCID
Onset of clear symptoms of psychosis to the initiation of antipsychotic medications.	CORS
Onset of psychosis (first week with sx corresponding to a PANSS score of ≥4 or on positive subscale items 1, 3, 5 or 6 or on the general subscale item 9) until start of adequate treatment (structured treatment with antipsychotic medications or hospitalization in a highly staffed psychiatric ward to manage psychotic sx,).	SCID
First onset of positive symptoms to index admission	PSE-9
Onset of overt hallucinations or delusions, up to the initiation of treatment with antipsychotic medication.	SCID
Appearance of at least one psychotic sx until initiation of adequate treatment	SCAN & IRAOS.
Onset of psychotic sx and the time that treatment was initiated.	SCID-P
Onset of the first positive sx to the first hospitalization.	SCID
Onset of positive symptoms to first admission.	MINI
Age of onset of psychosis tp age at initiation of antipsychotic treatment.	SCID/ KID-SCID
Onset of psychotic symptoms to service entry.	RPMIP
First manifestation of any positive psychotic sx to the start of antipsychotic treatment.	SCAN interview
Onset of psychotic symptoms to the first prescription of neuroleptics for psychotic symptoms and the first prescription of neuroleptics for psychosis	NS

Table 1. Summary of the 16 included first episode studies

Study Inclusion period	N Base-line	Gender		Age at onset (SD)		Mean DUP in weeks (SD)	Median DUP in weeks	N at short term follow-up (12-24 months)	N at long term follow-up (60-96 months)
		M	F	M	F				
Addington(22) (Jan. 1997-Dec. 2000)	240	161	79	23.4 (6.7)	26.4 (10.3)	77.1 (134.0)	26.0	199	50
Barnes (23;24) (Feb 1995-Oct 2001)	98	75	23	23.5 (6.6)	27. 2 (8.3)	54.0 (88.1)	20.0	96	-
Chen (26) (Sept. 1997-March 2000)	93	42	51	29.0 (9.2)	33.0 (9.7)	44.4 (135.7)	25.7	93	-
Clarke (27) (Febr.1995-	152	96	56	27.8 (6.4)	26.6 (8.3)	71.0 (115.9)	23.6	-	94
Febr. 1999) Craig (28) (1989-1995)	354	194	160	28.6 (15.8)	30.3 (11.9)	66.4 (186.2)	3.6	258	-
Cullberg(30;31) (Jan. 1996-Dec. 1997)	175	97	78	25.3 (6.4)	29.4 (7.1)	66.4 (163.2)	3.6	-	122
Drake (47) (34) (July 1996 – aug. 1998)	255	176	79	28.0 (9.9)	32.2 (10.7)	38.7 (82.2)	12.0	182	-
Gorna(35) (1988-2002)	86	34	52	26.6 (7.0)	23.6 (4.6)	40.4 (57.0)	12.9	83	74
Harris (36) (March 1989-July 1997)	318	216	102	21.7 (4.1)	23.9 (5.2)	24.1 (50.1)	5.8	295	135
Malla(40) (January 1997-July 2003)	153	116	37	22.8 (7.2)	28.9 (12.0)	70.9 (110.3)	23.9	-	-
Manchanda (41) (May 1996 – Dec. 2001)	122	93	29	22.1 (6.3)	28.8 (11.2)	70.7 (120.6)	21.6	122	-
Melle (42) (Jan.1997-Dec. 2000)	301	176	125	25.1 (7.9)	29.4 (11.2)	47.4 (117.7)	9.0	271	-
Montague (43) (1986-1988)	109	51	58	26.7 (6.8)	28.1 (8.3)	28.9 (88.1)	20.0	-	-
Petersen (45) (Jan. 1998-Dec. 2000)	578	235	343	24.3 (6.6)	24.5 (6.1)	106.0 (177.2)	34.4	394	247
Ucok(48) (> 1996)	148	84	64	23.3 (6.2)	25.6 (9.3)	32.8 (39.5)	17.1	54	-
Wunderink (52) (Okt. 2001-Dec. 2002)	157	113	44	25.6 (6.0)	28.8 (7.2)	46.0 (111.6)	4.4	120	105
Overall	3339	1959	1380	25.0 (8.6)	27.3 (9.2)	M 61.0 (125.5) F 61.9 (142.4)	13.3	1268 M 899 F	458 M 369 F

M = male
F = female

ASSOCIATION BETWEEN DURATION OF UNTREATED PSYCHOSIS AND NEGATIVE SYMPTOMS

Figure 1 shows a summary of the correlations between DUP and negative symptoms at baseline and short (1-2 years) and long-term follow-up (5-8 years). The data show a statistically significant positive correlation between DUP and negative symptoms at baseline (Fisher's z= 0.117 95%CI 0.064-0.17, at short-term follow-up (Fisher's z= 0.18 95%CI 0.086-0.274) and at long-term follow-up (Fisher's z= 0.202 95%CI 0.137- 0.267). There is no evidence for attenuation in the strength of the association with longer follow up. Tests for heterogeneity showed that the studies were low to moderately heterogeneous (I^2=48% at baseline, 75.9% at short term, 27.3% at long term follow-up). As a sensitivity analysis the reported Spearman correlation's where added to the meta-analysis at short term follow-up from the who studies on which IPD were not obtained (48;50;61). These two additional studies did not substantially alter the reported correlations of heterogeneity statistics (I^2=71.8%).

PREDICTED NEGATIVE SYMPTOM CHANGE

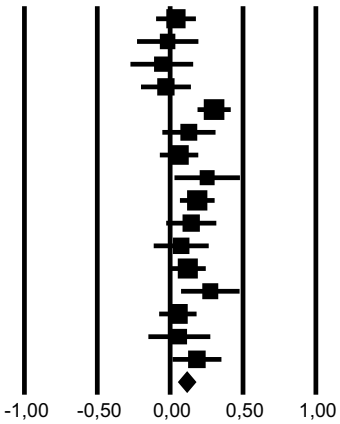
2150 patients nested in 12 studies were included in the multilevel analysis to explore for the effect of DUP on negative symptom reduction at short-term follow-up. The mean follow-up assessment was 15.5 months (95%CI 15.3-15.7). In the multilevel analysis for long-term follow-up, 795 individuals nested in 7 studies were included and the mean follow-up assessment was 71.4 months (95%CI 70.2-72.7).

Figures 2. and 3. show the percentage change in negative symptoms predicted by a given DUP at short and long-term follow-up respectively.

Figure 1.Summary of correlations between DUP and negative symptoms at baseline and short and long term follow up.

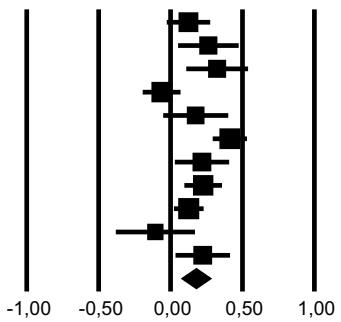
Correlation between DUP and negative symptoms at baseline

Study name	Fisher's Z	Standard error	Variance	Lower limit	Upper limit
Addington (2004)	0,040	0,066	0,004	-0,088	0,168
Barnes (2000)	-0,017	0,103	0,011	-0,219	0,185
Chen (2005)	-0,057	0,105	0,011	-0,264	0,150
Clarke (2006)	-0,029	0,083	0,007	-0,192	0,134
Craig (2000)	0,302	0,054	0,003	0,197	0,407
Cullberg (2002)	0,129	0,089	0,008	-0,045	0,303
Drake (2000)	0,061	0,063	0,004	-0,063	0,185
Gorna (2008)	0,254	0,110	0,012	0,038	0,471
Harris (2005)	0,186	0,056	0,003	0,076	0,297
Malla (2007)	0,145	0,083	0,007	-0,018	0,308
Manchanda (2005)	0,076	0,092	0,008	-0,104	0,257
Melle (2004)	0,122	0,059	0,003	0,007	0,236
Montague (1989)	0,276	0,098	0,010	0,084	0,468
Petersen (2005)	0,053	0,061	0,004	-0,067	0,173
Ucok (2006)	0,063	0,104	0,011	-0,141	0,267
Wunderink (2006)	0,184	0,081	0,007	0,025	0,344
	0,117	0,027	0,001	0,064	0,170



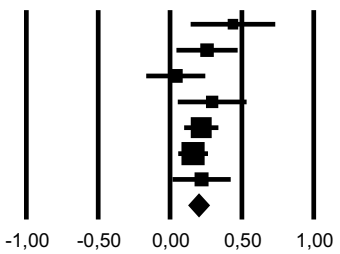
Correlation between DUP and negative symptoms at short term follow-up (1-2 year)

Study name	Fisher's Z	Standard error	Variance	Lower limit	Upper limit
Addington (2004)	0,125	0,073	0,005	-0,018	0,267
Barnes (2000)	0,263	0,103	0,011	0,061	0,465
Chen (2000)	0,324	0,105	0,011	0,117	0,530
Craig (2000)	-0,062	0,063	0,004	-0,185	0,061
Gorna (2008)	0,175	0,111	0,012	-0,043	0,393
Harris (2005)	0,412	0,056	0,003	0,301	0,522
Manchanda (2005)	0,218	0,092	0,008	0,038	0,399
Melle (2004)	0,227	0,062	0,004	0,105	0,349
Petersen (2005)	0,127	0,048	0,002	0,032	0,222
Ucok (2006)	-0,105	0,136	0,019	-0,372	0,161
Wunderink (2006)	0,224	0,092	0,009	0,042	0,405
	0,180	0,048	0,002	0,086	0,274



Correlation between DUP and negative symptoms at long term follow-up (5-8 year)

Study name	Fisher's Z	Standard error	Variance	Lower limit	Upper limit
Addington (2004)	0,438	0,146	0,021	0,152	0,724
Clarke (2000)	0,258	0,104	0,011	0,053	0,462
Cullberg (2002)	0,040	0,101	0,010	-0,157	0,237
Gorna (2008)	0,293	0,118	0,014	0,062	0,524
Harris (2005)	0,217	0,056	0,003	0,107	0,328
Petersen (2005)	0,160	0,048	0,002	0,066	0,255
Wunderink (2006)	0,219	0,099	0,010	0,025	0,414
	0,202	0,033	0,001	0,137	0,267



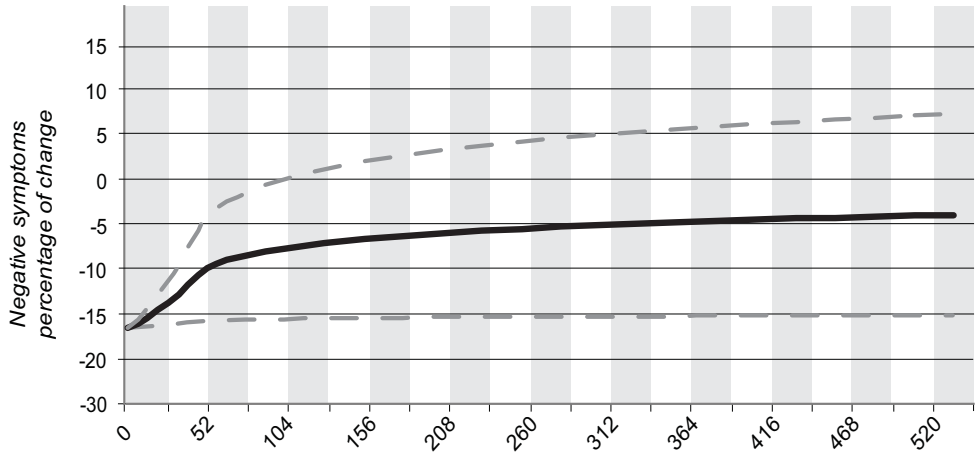


Figure 2. Predicted change in negative symptoms after short term follow-up (1-2 years) against duration of untreated psychosis in weeks (with 95% CIs)

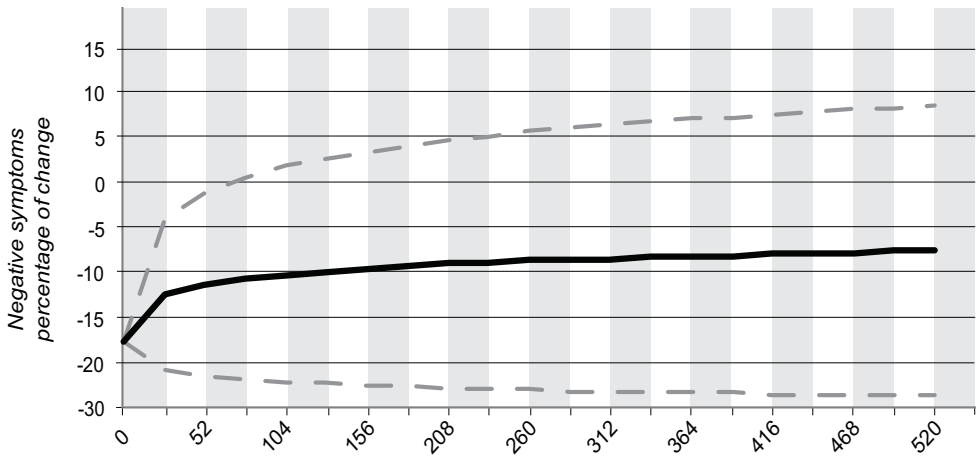


Figure 3. Predicted change in negative symptoms after longer term follow-up (5-8 years) against duration of untreated psychosis in weeks (with 95% CIs)

DISCUSSION

The review has shown that there is a significant positive association between DUP and negative symptoms at: baseline, short (1-2 years) and long-term (5-8 years) follow-up. The effect is non-linear, so that a reduction in DUP in someone with a shorter DUP (i.e. less than 9 months) has a greater impact on negative symptoms than the same reduction in someone with a DUP greater than nine months. These findings are in accordance with the findings of the TIPS study and the study of Malla and colleagues (54;55), both of which suggested that reduction of DUP may be as important for improving the severity of negative symptoms as it is for positive symptoms (56). Our finding of a non-linear association between DUP and negative symptoms is similar to that reported by Drake et al. for total PANSS scores (34) albeit in a small sample with a short follow-up.

The association between a longer DUP and persistence of negative symptoms (after 1-2 years) is consistent with the hypothesis that in many cases psychosis is a clinical manifestation of a progressive pathological process in which early detection and intervention could be effective in ameliorating the course of the disorder. Figure 2 and 3 suggest that the existence of a critical period of DUP of about 9 months in which the association with negative symptoms is particularly strong. This finding supports arguments for early detection and intervention programs, as other than prevention, there is no evidence-based treatment for negative symptoms (56). However, it is important to emphasize that this analysis does not prove that there is a causal association between negative symptoms and DUP.

As a result of obtaining individual patient data, this review has substantially increased the amount of information available for analysis. Consequently, it has extended the findings of previous meta-analyses by: providing more precise estimates of the correlation between duration of untreated psychosis and negative symptoms, examining the correlation at both short and long-term follow up; and exploring the linearity of the association. This is of clinical importance because the window of opportunity to intervene to improve the prognosis of psychosis is considered to last 3-5 years (57).

The main limitation 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, they did not substantially alter the reported correlations of heterogeneity statistics.

Hence, the conclusions of the meta-analysis presented here are probably not substantially compromised by the exclusion of those studies.

Previous studies have noted considerable variation in first episode psychosis cohorts (58), for example in: participant characteristics; instruments to assess symptoms; and definitions of DUP. Despite these issues, this analysis detected only a mild to moderate degree of statistical heterogeneity between studies, at a level that was not sufficient to undermine the main findings. We conducted a funnel plot in order to test publication bias. The plot shows the presence of symmetry for all analysis. Since the sampling error is random, this underpins the idea that there is no substantial publication bias.

In summary, the relationship between DUP and negative symptoms has been underestimated, and is in fact strong and persistent. A DUP of less than 9 months appears to be a strong predictor of improvement of negative symptoms, while most patients with a DUP longer than 9 months show persistent negative symptoms. The absence of substantially effective treatments for negative symptoms supports reducing DUP as an important option for ameliorating negative symptoms.

AUTHOR DISCLOSURE

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There was no funding for this study.

CONTRIBUTORS

Nynke Boonstra designed the study and wrote the protocol together with Rianne Klaassen and Lex Wunderink. Together they performed the literature searches and analysis. Max Marshall supported the analysis and interpretation, Sjoerd Sytema, Lieuwe de Haan and Durk Wiersma read and revised the manuscript. All authors contributed to and have approved the final manuscript.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

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REFERENCE LIST

(1) Blanchard JJ, Horan WP, Collins LM. Examining the latent structure of negative symptoms: is there a distinct subtype of negative symptom schizophrenia? Schizophr Res 2005; 77(2-3):151-165.

(2) Kirkpatrick B, Fenton WS, Carpenter WT, Jr., Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull 2006; 32(2):214-219.

(3) Makinen J, Miettunen J, Isohanni M, Koponen H. Negative symptoms in schizophrenia: a review. Nord J Psychiatry 2008; 62(5):334-341.

(4) Malla AK, Norman RM, Takhar J, Manchanda R, Townsend L, Scholten D et al. Can patients at risk for persistent negative symptoms be identified during their first episode of psychosis? J Nerv Ment Dis 2004; 192(7):455-463.

(5) Heydebrand G, Weiser M, Rabinowitz J, Hoff AL, DeLisi LE, Csernansky JG. Correlates of cognitive deficits in first episode schizophrenia. Schizophr Res 2004; 68(1):1-9.

(6) Addington J, Addington D. Premorbid functioning, cognitive functioning, symptoms and outcome in schizophrenia. J Psychiatry Neurosci 1993; 18(1):18-23.

(7) Petersen L, Thorup A, Oqhlenschlaeger J, Christensen TO, Jeppesen P, Krarup G et al. Predictors of remission and recovery in a first-episode schizophrenia spectrum disorder sample: 2-year follow-up of the OPUS trial. Can J Psychiatry 2008; 53(10):660-670.

(8) Schmitz N, Malla A, Norman R, Archie S, Zipursky R. Inconsistency in the relationship between duration of untreated psychosis (DUP) and negative symptoms: sorting out the problem of heterogeneity. Schizophr Res 2007; 93(1-3):152-159.

(9) Malla AK, Takhar JJ, Norman RM, Manchanda R, Cortese L, Haricharan R et al. Negative symptoms in first episode non-affective psychosis. Acta Psychiatr Scand 2002; 105(6):431-439.

(10) Pogue-Geile MF, Harrow M. Negative symptoms in schizophrenia: their longitudinal course and prognostic importance. Schizophr Bull 1985; 11(3):427-439.

(11) Herbener ES, Harrow M. Longitudinal assessment of negative symptoms in schizophrenia/schizoaffective patients, other psychotic patients, and depressed patients. Schizophr Bull 2001; 27(3):527-537.

(12) Buckley PF, Stahl SM. Pharmacological treatment of negative symptoms of

schizophrenia: therapeutic opportunity or cul-de-sac? Acta Psychiatr Scand 2007; 115(2):93-100.

(13) Leucht S, Heres S, Kissling W, Davis JM. Evidence-based pharmacotherapy of schizophrenia. Int J Neuropsychopharmacol 2011;1-16.

(14) Castelein S, Bruggeman R, van Busschbach JT, van Der GM, Stant AD, Knegtering H et al. The effectiveness of peer support groups in psychosis: a randomized controlled trial. Acta Psychiatr Scand 2008; 118(1):64-72.

(15) Gold C, Solli HP, Kruger V, Lie SA. Dose-response relationship in music therapy for people with serious mental disorders: systematic review and meta-analysis. Clin Psychol Rev 2009; 29(3):193-207.

(16) Rohricht F, Priebe S. Effect of body-oriented psychological therapy on negative symptoms in schizophrenia: a randomized controlled trial. Psychol Med 2006; 36(5):669-678.

(17) Melle I, Larsen TK, Haahr U, Friis S, Johannesen JO, Opjordsmoen S et al. Prevention of negative symptom psychopathologies in first-episode schizophrenia: two-year effects of reducing the duration of untreated psychosis. Arch Gen Psychiatry 2008; 65(6):634-640.

(18) Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. Arch Gen Psychiatry 2005; 62(9):975-983.

(19) Perkins DO. Review: longer duration of untreated psychosis is associated with worse outcome in people with first episode psychosis. Evid Based Ment Health 2006; 9(2):36.

(20) Drake RJ, Haley CJ, Akhtar S, Lewis SW. Causes and consequences of duration of untreated psychosis in schizophrenia. Br J Psychiatry 2000; 177:511-515.

(21) Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet 1993; 341(8842):418-422.

(22) Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. Eval Health Prof 2002; 25(1):76-97.

(23) Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13(2):261-276.

(24) Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS):

conceptual and theoretical foundations. Br J Psychiatry Suppl 1989;(7):49-58.

(25) Overall JE, Gorham DR. The brief psychiatric rating scale. Psychol Rep 1962; 10:799-812.

(26) Borenstein M, Hedges LV, Higgins JPT, Rowlands RP. Introduction to Meta-Analysis. John Whiley & Sons Ltd, The Atrium, Southern Gate, Chisterer, West Sussex, United Kingdom, 2009.

(27) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327(7414):557-560.

(28) STATA statisical software release 11.0. College Station, Texas, 2009.

(29) Snijders T.A.B. BRJ. Multi-level Analysis: An Introduction to Basis and Advances Multilevel Modeling. London: SAGE Publication, 1999.

(30) Addington J, Van Mastrigt S, Addington D. Duration of untreated psychosis: impact on 2-year outcome. Psychol Med 2004; 34(2):277-284.

(31) Barnes TR, Hutton SB, Chapman MJ, Mutsatsa S, Puri BK, Joyce EM. West London first-episode study of schizophrenia. Clinical correlates of duration of untreated psychosis. Br J Psychiatry 2000; 177:207-211.

(32) Black K, Peters L, Rui Q, Milliken H, Whitehorn D, Kopala LC. Duration of untreated psychosis predicts treatment outcome in an early psychosis program. Schizophr Res 2001; 47(2-3):215-222.

(33) Chen EY, Hui CL, Chan RC, Dunn EL, Miao MY, Yeung WS et al. A 3-year prospective study of neurological soft signs in first-episode schizophrenia. Schizophr Res 2005; 75(1):45-54.

(34) Clarke M, Whitty P, Browne S, McTigue O, Kamali M, Gervin M et al. Untreated illness and outcome of psychosis. Br J Psychiatry 2006; 189:235-240.

(35) Craig TJ, Bromet EJ, Fennig S, Tanenberg-Karant M, Lavelle J, Galambos N. Is there an association between duration of untreated psychosis and 24-month clinical outcome in a first-admission series? Am J Psychiatry 2000; 157(1):60-66.

(36) Crespo-Facorro B, Roiz-Santianez R, Pelayo-Teran JM, Gonzalez-Blanch C, Perez-Iglesias R, Gutierrez A et al. Caudate nucleus volume and its clinical and cognitive correlations in first episode schizophrenia. Schizophr Res 2007; 91(1-3):87-96.

(37) Cullberg J, Levander S, Holmqvist R, Mattsson M, Wieselgren IM. One-year

outcome in first episode psychosis patients in the Swedish Parachute project. Acta Psychiatr Scand 2002; 106(4):276-285.

(38) de Haan L, van Der GM, Wolthaus J. Duration of untreated psychosis and the long-term course of schizophrenia. Eur Psychiatry 2000; 15(4):264-267.

(39) Gorna K, Jaracz K, Rybakowski F, Rybakowski J. Determinants of objective and subjective quality of life in first-time-admission schizophrenic patients in Poland: a longitudinal study. Qual Life Res 2008; 17(2):237-247.

(40) Harris MG, Henry LP, Harrigan SM, Purcell R, Schwartz OS, Farrelly SE et al. The relationship between duration of untreated psychosis and outcome: an eight-year prospective study. Schizophr Res 2005; 79(1):85-93.

(41) Ho BC, Andreasen NC, Flaum M, Nopoulos P, Miller D. Untreated initial psychosis: its relation to quality of life and symptom remission in first-episode schizophrenia. Am J Psychiatry 2000; 157(5):808-815.

(42) Larsen TK, Moe LC, Vibe-Hansen L, Johannessen JO. Premorbid functioning versus duration of untreated psychosis in 1 year outcome in first-episode psychosis. Schizophr Res 2000; 45(1-2):1-9.

(43) Malla A, Norman R, McLean T, Scholten D, Townsend L. A Canadian programme for early intervention in non-affective psychotic disorders. Aust N Z J Psychiatry 2003; 37(4):407-413.

(44) Malla A, Schmitz N, Norman R, Archie S, Windell D, Roy P et al. A multisite Canadian study of outcome of first-episode psychosis treated in publicly funded early intervention services. Can J Psychiatry 2007; 52(9):563-571.

(45) Manchanda R, Norman R, Malla A, Harricharan R, Takhar J, Northcott S. EEG abnormalities and two year outcome in first episode psychosis. Acta Psychiatr Scand 2005; 111(3):208-213.

(46) Melle I, Larsen TK, Haahr U, Friis S, Johannessen JO, Opjordsmoen S et al. Reducing the duration of untreated first-episode psychosis: effects on clinical presentation. Arch Gen Psychiatry 2004; 61(2):143-150.

(47) Montague LR, Tantam D, Newby D, Thomas P, Ring N. The incidence of negative symptoms in early schizophrenia, mania and other psychoses. Acta Psychiatr Scand 1989; 79(6):613-618.

(48) Oosthuizen P, Emsley RA, Keyter N, Niehaus DJ, Koen L. Duration of untreated psychosis and outcome in first-episode psychosis. Perspective from a developing

country. Acta Psychiatr Scand 2005; 111(3):214-219.

(49) Petersen L, Jeppesen P, Thorup A, Abel MB, Ohlenschlaeger J, Christensen TO et al. A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. BMJ 2005; 331(7517):602.

(50) Sim K, Swapna V, Mythily S, Mahendran R, Kua EH, McGorry P et al. Psychiatric comorbidity in first episode psychosis: the Early Psychosis Intervention Program (EPIP) experience. Acta Psychiatr Scand 2004; 109(1):23-29.
(51) Ucok A, Polat A, Cakir S, Genc A. One year outcome in first episode schizophrenia. Predictors of relapse. Eur Arch Psychiatry Clin Neurosci 2006; 256(1):37-43.

(52) Verdoux H, Liraud F, Bergey C, Assens F, Abalan F, van Os J. Is the association between duration of untreated psychosis and outcome confounded? A two year follow-up study of first-admitted patients. Schizophr Res 2001; 49(3):231-241.

(53) Vyas NS, Hadjulis M, Vourdas A, Byrne P, Frangou S. The Maudsley early onset schizophrenia study. Predictors of psychosocial outcome at 4-year follow-up. Eur Child Adolesc Psychiatry 2007; 16(7):465-470.

(54) Wade D, Harrigan S, Edwards J, Burgess PM, Whelan G, McGorry PD. Patterns and predictors of substance use disorders and daily tobacco use in first-episode psychosis. Aust N Z J Psychiatry 2005; 39(10):892-898.

(55) Wunderink A, Nienhuis FJ, Sytema S, Wiersma D. Treatment delay and response rate in first episode psychosis. Acta Psychiatr Scand 2006; 113(4):332-339.

(56) Yamazawa R, Nemoto T, Kobayashi H, Chino B, Kashima H, Mizuno M. Association between duration of untreated psychosis, premorbid functioning, and cognitive performance and the outcome of first-episode schizophrenia in Japanese patients: prospective study. Aust N Z J Psychiatry 2008; 42(2):159-165.

(57) Birchwood M. Early intervention and sustaining the management of vulnerability. Aust N Z J Psychiatry 2000; 34 Suppl:S181-S184.

(58) Barnes TR, Leeson VC, Mutsatsa SH, Watt HC, Hutton SB, Joyce EM. Duration of untreated psychosis and social function: 1-year follow-up study of first-episode schizophrenia. Br J Psychiatry 2008; 193(3):203-209.

(59) Flyckt L, Mattsson M, Edman G, Carlsson R, Cullberg J. Predicting 5-year outcome in first-episode psychosis: construction of a prognostic rating scale. J Clin Psychiatry 2006; 67(6):916-924.

(60) de Haan L, Linszen DH, Lenior ME, de Win ED, Gorsira R. Duration of untrea-

ted psychosis and outcome of schizophrenia: delay in intensive psychosocial treatment versus delay in treatment with antipsychotic medication. Schizophr Bull 2003; 29(2):341-348.

(61) Subramaniam M, Pek E, Verma S, Chan YH, Chong SA. Diagnostic stability 2 years after treatment initiation in the early psychosis intervention programme in Singapore. Aust N Z J Psychiatry 2007; 41(6):495-500.

CHAPTER 5

Association of treatment delay, migration and urbanicity in psychosis

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ABSTRACT

BACKGROUND

Several factors may contribute to duration of untreated psychosis (DUP): patient-delay, referral-delay and treatment-delay caused by mental health care services (MHS-delay). In order to find the most effective interventions to reduce DUP, it is important to know what factors in these pathways to care contribute to DUP.

AIM

To examine the relationship of the constituents of treatment delay, migration status and urbanicity.

METHOD

In first episode psychotic patients (N=182) from rural, urban and highly urbanized areas, DUP, migration status and pathways to care were determined.

RESULTS

Mean DUP was 53.6 weeks (median 8.9, SD=116.8). Patient-delay was significantly longer for patients from highly urbanized areas and for first generation immigrants. MHS-delay was longer for patients who were treated already by MHS for other diagnoses.

CONCLUSIONS

Specific interventions are needed focusing on patients living in highly urbanized areas and first generation immigrants in order to shorten patient delay. MHS should improve early detection of psychosis in patients already in treatment for other diagnosis.

Keywords: treatment delay- DUP- early intervention - migration – first episode - urbanicity

INTRODUCTION

The duration of untreated psychosis (DUP) is defined as the time from manifestation of the first psychotic symptoms to initiation of appropriate treatment (59). Over the past ten years evidence accumulated on the association of shorter DUP and a better outcome on several measures (60-63). Several demographical factors influencing DUP have been suggested earlier. DUP is repeatedly found to be shorter when there is an acute mode of onset of the illness (64-66) or when the patient is employed or studying when the illness emerges (67;68). The literature is less consistent on the issue of active family involvement in help-seeking. Morgan and colleagues reported a shorter DUP whereas Compton and colleagues showed a longer duration (69;70). Norman et al. reported the interesting finding that patients with an ongoing contact with professional care givers before and during the onset of psychosis had longer delays from first service contact after onset to initiation of adequate treatment (71).

Brunet et al define DUP as the sum of three components; the delay in help-seeking by the patient, the referral delay, e.g. by the general practitioner, and thirdly delay in recognition and treatment by mental health care services (72). The main object of the present study is to examine the various components of treatment delay in a representative sample of first episode psychotic patients in the Netherlands. Since migration status has been shown to be associated with longer patient delay and the various pathways to care might differ between rural and more urbanized area's this study was designed to examine the relationship between DUP, migration status and urbanicity (73;74). Understanding where in the pathways to care the delay occurs and who run the highest risk may help finding more effective interventions to reduce DUP.

MATERIAL AND METHODS

SUBJECTS

The study was conducted in two mental health care services in the Netherlands each with an early intervention program for psychosis; geographically covering the province of Friesland and the city of Amsterdam. The basic organisation of mental health services in Amsterdam and Friesland is similar. Both areas have implemented early detection and intervention for psychosis and for patients with an at risk mental state for psychosis. Referral by a GP is the standard route for referral to MHS, although self referral (mostly via emergency services) is possible in both areas. Inclusion took place from May 2008 through September 2009. Inclusion criteria were a DSM-IV diagnosis of a non-affective psychotic disorder, no appropriate treatment with antipsychotic medication so far and an age between 10 and 36 years. We excluded patients with a substance induced psychotic disorder or patients with a neurological or endocrine disorder possibly related to the psychosis.

The population in the catchment area amounted to 1.4 million. The province of Friesland is a mixed rural- urban area with about 645,000 inhabitants and a mean population density of 192/km² on January 1st 2009, of whom 25.000 (3.9%) where first generation immigrants and 28.000 (4.3%) second generation immigrants. The population at risk (10-36 years of age) in Friesland was 204,700 inhabitants. The city of Amsterdam is an highly urbanized area with a mean population density of 4493/ km². Its number of inhabitants was 755,600 on January 1st 2009 of whom 214.000 (28.3%) were first generation and 160.000 (21.2%) were second generation immigrants. The population at risk was 299,600 inhabitants. The early intervention programs in both areas provide comprehensive treatment to patients suffering from a first episode psychosis, inpatient as well as outpatient care.

MEASURES

The assessment protocol included completion of a validated semi-structured interview to establish DSM-IV diagnosis shortly after intake, by means of the mini- Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (75) or Comprehensive Assessment of Symptoms and History (CASH) (76). Information regarding DUP was collected using the Dutch translation of the Nottingham Onset Schedule (NOS), with the same definitions as proposed by Singh and colleagues (77). The NOS was developed to systematically determine the onset of prodromal and psychotic symptoms and the start of antipsychotic medication or intensive treatment. For all first contact patients with a psychotic disorder, the onset of the first psychotic episode, dates of first contact with primary health care, referral to MHS and initiation of appropriate antipsychotic treatment and intensive treatment were collected based on all available data sources; including a semi-structured personal interview with the patient and relatives, and information from medical files. If only a year was known, the first of July of that year was noted as a date, when only a month was known, the 15th of that month was noted. In addition to this, data on date of birth, age at onset of psychosis, postal code, and nativity were collected.

The definition of the different components of DUP - patient delay, referral delay and delay within MHS – are specified in table 1. To determine nativity we used the classification of the Netherlands' Bureau of Statistics (https://statline.cbs.nl). If a patient or one of his or her parents was born in another country, then the patient was assigned to the nativity group that fitted that foreign country. In case of parents born in different countries, the country of birth of the mother was used. When a patient and at least one of his or her parents were born in another country, then the patient was classified as a first generation immigrant. If a patient was born in the Netherlands but at least one of his or her parents was born in another country, the patient was classified as a second generation immigrant. This definition of nativity implies that the "native-born" group includes third generation immigrants (i.e. those with parents born in The Netherlands but grandparents not). With respect to urbanicity we divided our study population in three subgroups. Patients were assigned to highly urban area when they lived in the city of Amsterdam (> 750.000 inhabitants), patients where assigned

to an urban area when they lived in a town (about 100.000 inhabitants) and the third group consisted of patients living in a rural area.

Table 1. Definitions

DUP	The time (days) between the first experience of psychotic symptoms for more than one week and the initiation of appropriate treatment.
Patient delay	The time (days) between the first experience of psychotic symptoms for more than one week and first contact with a professional health care worker, e.g. a GP.
Referral delay	The time (days) between first contact with a professional health care worker and referral to MHS.
Delay within MHS	The time (days) between referral to MHS and initiation of appropriate treatment.
Psychotic symptoms	A PANSS score of 4 or more on at least one of the items 1 (delusions), 3 (hallucinatory behaviour), 5 (grandiosity), 6 (suspiciousness/persecution) or 9 (unusual thought content).
Appropriate treatment	The use of antipsychotic medication for at least one month and/or the start of intensive treatment. If so, the first day of receiving medication or the first day of start of intensive treatment was noted as start of appropriate treatment. Whatever was first.
Intensive treatment	Frequent contacts with patient and their family, psycho-education and rehabilitation. The first day of this intensive treatment was noted as start of intensive treatment.

STATISTICAL ANALYSIS

All analysis were performed by the use of SPSS 17.0. Mean and median DUP was calculated for all components of DUP and for the overall DUP. Because of the skewed distribution of DUP we used non-parametric statistical analysis if DUP was one of the variables tested. Mann Whitney U tests were used to assess whether distributions of DUP were equal for 2 different groups and Kruskal Wallis tests were used to test for equality of median DUP of more than two groups. We used a generalized linear model (GLM), acknowledging the Gamma distribution of DUP, to assess confounding.

RESULTS

A total number of 182 patients was included in the study. A summary of patients' characteristics is presented in table 2. The mean age at onset for males was 21.8 years ± 4.9 (SD) and for females 22.5 years ± 5.8 (SD), difference in age at onset was not significant.

DUP

Mean total DUP for all patients (N=182) was 53.6 weeks ± 116.8 (SD). The median DUP was 8.9 weeks, (Q1 = 2.0 and Q3 = 47.8, range 0-874). Figure 1 gives an overview of the distribution.

Mean patient delay was 32.4 weeks ± 100.4 (SD) with a median of 0.5 weeks and a range from 0 day to 16 years (Q1 = 0.0 and Q3 = 12.7 weeks). Patient delay for 19 patients was zero because they had already been in mental health care treatment for another diagnosis at onset of first episode psychosis. The mean referral delay was 5.6 weeks ± 23.9 weeks (SD) with a median of 0.0 weeks (range: 0-23; Q1 = 0.0 and Q3 = 1.9 weeks). The mean delay in mental health care services (MHS) was 15.6 weeks ± 42.6 (SD) with a median of 0.9 weeks (range: 0-300; Q1 = 0.0 and Q3 = 6.7 weeks).

The majority of patients (53.3%, n=97) were referred to MHS by a general practitioner (GP). 54 patients (29.7%) came into contact with MHS via emergency services, 4 patients (2.2%) were referred by other medical professionals like a general hospital or youth health service, 8 patients (4.4%) were referred by non medical professionals like religious institutions or relatives and 19 patients (10.4%) had already been under treatment by a mental health care service for another diagnosis when the first psychotic symptoms emerged.

The mean referral delay due to GP's was 10.2 weeks (± 32.1) with a median of 0.6 weeks while this was 0.3 weeks (±1.3) with a median of zero weeks for emergency services, and 0.8 weeks (± 1.1) for other medical professionals. Patients who came in contact with MHS via their GP had significantly longer referral delay than patients who where referred by emergency services or other medical professionals (Kruskal-Wallis χ 2 = 30.7, df =2, $p < .001$).

Table 2. Sample characteristics (N=182)

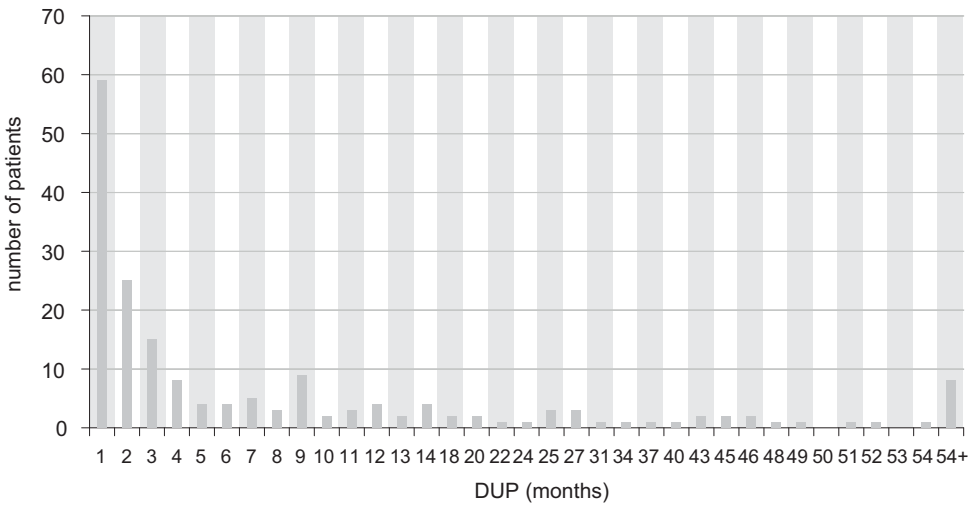
		N *	
Mean age at onset of first episode psychosis		21.9 years (SD ± 5.1)	
Gender			
	Male	140	(76.9%)
	Female	42	(23.1%)
Diagnosis			
	Schizophrenia	89	(48.9%)
	Psychotic disorder NOS	57	(31.3%)
	Brief psychotic disorder	5	(2.7%)
	Schizoaffective disorder	15	(8.2%)
	Schizophreniform disorder	16	(8.8%)
Residential Area (urbanicity)			
	Extremely urban (city)	99	(54.4%)
	Urban (town)	38	(20.9%)
	Rural	45	(24.7%)
Nativity			
	Dutch	102	(56.0%)
	First generation immigrants	49	(27.0%)
	Second generation immigrants	31	(17.0%)

* numbers unless otherwise specified

The 19 patients who had already been under treatment in mental health care services at the time of onset of psychotic symptoms, had a mean MHS delay of 25.2 weeks ± 32.4 (SD) with a median of 13.1 weeks.

The mean MHS delay for the other 163 patients was 14.5 weeks (± 43.6), with a median of 0.3 weeks. Median MHS delay was significantly longer for patients who where already treated by mental health care services compared to all other patients (MW U: 730, Z=-3.9, p <.001).

Figure 1. Distribution of DUP (N=182)



54+; 60, 62, 64, 66, 81, 133, 197, 202 months (one in each of these months)

There were no significant differences in pathways to care between males and females (patient delay MW U: 2679, Z -0.93, p=0.36; referral delay MW U: 2658, Z -1.08, p=0.28; MHS delay MW U: 2861, Z -0.28, p=0.78) and there was also no significant difference in the overall DUP between the various referrers (Kruskal-Wallis χ 2 = 5.7, df= 4, p=.22).

Table 3. shows the means and contribution of the different components of DUP for native-borns, first and second generation immigrants in rural, urban and highly urbanized areas. DUP was significantly longer for patients living in a highly urbanized area (Kruskal-Wallis X^2= 4.0, df=2, p=.046) and this was mainly due to a longer patient delay. Patients from rural areas had long MHS delay in contrast to patients from urban and highly urbanized areas, this difference was not significant (Kruskal-Wallis X^2= 2.9, df=2, p=.089). First generation immigrants had significantly longer overall DUP than native-born patients and second generation immigrants (Kruskal-Wallis X^2= 6.2, df=2, p=.045). First generation immigrants from highly urbanized area had the longest patient delay with a mean of 88.1 weeks (SD 186.6) and this was 89% of overall DUP (99.4 weeks, SD 185.7) in this group. Although it seems that first generation immigrants from rural and urban areas suffer less pronounced patient delay and longer MHS delay than native-borns, differences in DUP components between migration status groups were not significant when tested with a Kruskal-Wallis test.

Since migration status and urbanicity are strongly correlated (phi coefficient: 0.411, p<.001) we conducted a GLM to assess the effects on DUP. The result of this GLM showed that only migration status, remained a significant predictor, even after controlling for age of onset and sex (p=0.01).

First and second generation immigrant patients were more likely to be referred to MHS by emergency services than native-born patients (X^2= 7.30, df=1, p=.007) and second generation immigrants were referred by emergency services more often than first generation immigrants (X^2= 4.64, df=1, p= .031).

Table 3. Contribution of components of DUP on overall DUP for native-borns, first and second immigrant patients living in rural, urban or highly urbanized areas (N=182)

	Patient delay			Referral delay			MHS delay			Overall DUP Mean * (SD)
	Mean* (SD) (% of overall DUP)		Median	Mean* (SD) (% of overall DUP)		Median	Mean* (SD) (% of overall DUP)		Median	
Rural (N=45)	12.9 (34.1)	33%	0.0	5.2 (16.9)	13%	0.0	21.2 (49.5)	54%	2.0	39.2 (63.5)
Native-borns (n=37)	10.9 (28.7)	33%	0.0	4.9 (16.8)	15%	0.0	17.3 (41.4)	52%	2.0	33.1 (57.5)
First generation immigrants (n=8)	22.0 (54.5)	32%	0.9	6.6 (18.4)	10%	0.0	39.0 (78.2)	58%	5.8	67.7 (85.1))
Second generation immigrants (N=0)	--		--	--		--	--		--	--
Urban (N=38)	8.5 (20.5)	29%	0.0	7.3 (37.4)	25%	0.0	13.8 (31.0)	47%	0.4	29.6 (54.0)
Native-borns (n=28)	9.9 (23.4)	39%	0.0	9.5 (43.6)	37%	0.0	6.2 (13.6)	24%	0.0	25.5 (54.3)
First generation immigrants (n=10)	4.6 (8.7)	11%	0.0	1.2 (2.8)	3%	0.0	35.1 (52.1)	86%	4.1	40.9 (54.4)
Second generation immigrants (n=0)	--			--			--			--
Highly urban (N=99)	50.5 (131.1)	73%	2.0	5.1 (20.0)	7%	0.0	13.8 (43.2)	20%	0.4	69.4 (147.3)
Native-borns (N=37)	22.3 (52.7)	53%	2.0	8.3 (31.2)	20%	0.0	11.3 (31.8)	27%	0.0	41.9 (64.5)
First generation immigrants (n=31)	88.1 (186,6)	89%	4.4	5.4 (10.1)	5%	0.3	5.9 (10.7)	6%	2.4	99.4 (185.7)
Second generation immigrants (n=31)	46.5 (124.7)	64%	0.6	0.8 (2.0)	1%	0.0	24.9 (67.7)	34%	0.0	72.3 (172.0)
Overall	32.4 (100.4)	60%	0.5	5.6 (23.9)	10%	0.0	15.6 (42.6)	29%	0.9	53.6 (116.8)

*All means and SD's are presented in weeks

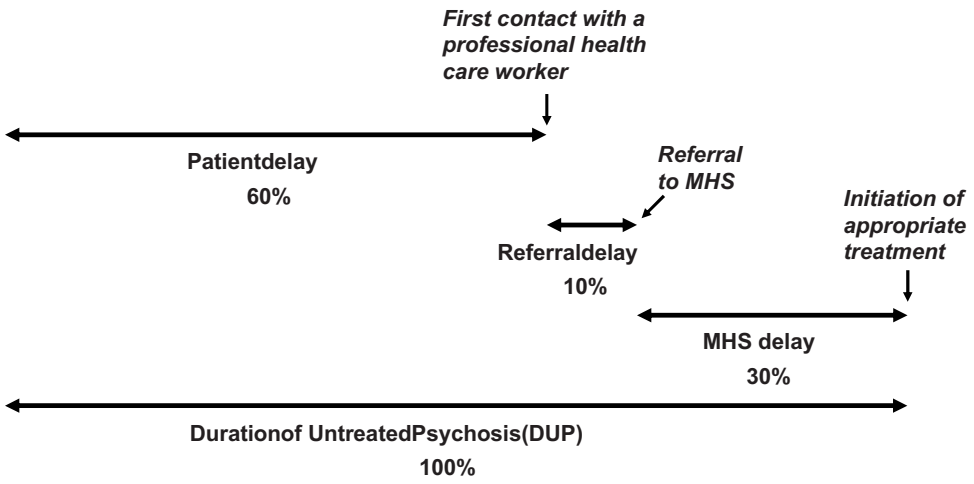


Figure 2. DUP components
MHS= Mental Health care Services

DISCUSSION

Mean and median overall DUP found in this study (53.6 weeks and 8.9 weeks respectively) is shorter than mean DUP of about one or two years and the average median DUP of 26 weeks reported in most other studies (78) but in accordance with a recent Dutch multi centre study in which a mean DUP of 1 year and a median DUP of 1 month was found (79). An explanation for this relative short mean and median DUP might be explained by the early intervention programs implemented in the areas of the study as well as services for detection of ultra high risk subjects (80). Specialized services for detecting ultra high risk subjects have shown to play a role in reducing DUP (81).

This study found that first generation immigrant patients have longer overall DUP than native-born and second generation immigrant patients. In addition first and second generation immigrant patients have a greater chance to enter mental health care services by emergency services compared to native-born patients, a finding that concurs with a British study, where Morgan and colleagues have shown that being a member of a black minority increased the chance to reach specialized services via non-health professionals (82). Several possible explanations for an association between longer DUP and non-native-born background have been proposed. First generation immigrants may be less acquainted with the concept of mental illness and the mental health services (83). Also feelings of shame and fear for stigma may be more pronounced and first generation immigrants might be more likely to seek help from religious or alternative healers first (84). Finally these individuals are more likely not to be fluent in Dutch and this language barrier may also cause delay. It is plausible to suggest that these factors diminish in following generations.

DUP was longest for patients living in a highly urbanized area and this was mostly due to a longer patient delay. Living in a highly urbanized area is confounded with immigration status and this has an influence on the correlation of urbanicity and DUP as shown in the GLM analysis. Nevertheless, native-born patients living in a highly urbanized area seem to have a longer patient delay and overall DUP too.

MHS delay was significantly longer for patients from rural areas as compared to patients living in urban and highly urbanized areas. The longest MHS delay was seen in immigrants from rural and urban areas. Despite the fact that this difference did not reach statistical significance in this study, this might be an important issue in the light of the already longer overall DUP seen in immigrants. Because the incidence of psychotic disorders is higher in urban and highly urbanized areas, clinicians in these areas might be more familiar with the detection of psychotic symptoms and start appropriate treatment earlier. And this effect may be even more pronounced in immigrants living in rural and urban areas. This factor could explain at least part of the differences in treatment delay caused by mental health care services. The basic

organisation of mental health services in Amsterdam and Friesland is similar. Differences in delay of referral to MHS and delay within MHS are unlikely to be caused by mental health services organisation. Systematic screening instruments for emerging psychosis improve the detection of first episode psychotic patients and thereby shorten MHS delay (85).

Since a GP is the final referring agency in most cases (53%), GP's might play an important role in the pathway to care for psychosis although most GP's not even see a first episode psychotic patient every year (86). In addition delay due to waiting lists in MHS is attributed to referral delay. There was no association between the referrer source and the overall DUP. A recent meta analysis shows inconsistent results (87); some studies show longer DUP for patients who were referred by a GP while other studies report a shorter DUP for patients referred by a GP. In this study the referral delay due to a GP was significantly longer than the delay due to other referrers.

The finding that patients who developed a psychosis while in the care of mental health care services have a long delay is in accordance with earlier findings in Canada (88). Norman et al showed that one can not assume that once contact with mental health care services occurs an expedited pathway to treatment of psychotic disorder will follow. Those patients seem to be at particular risk of treatment delay. This calls for systematic re-evaluation of diagnosis during treatment of any type of disorder at mental health care services (85;89).

Contact with (MHS) emergency service is the fastest route to appropriate treatment. Yet it is not a preferred route, as these patients often have a long patient delay, possibly related to the fact that patients entering treatment through this route demonstrate a more severe symptom profile (90). The finding that first and second generation immigrant patients have a greater chance to enter via emergency services is supported by the study of Snowden et al. (91) and this is also in accordance with the previously reported findings from Canada (92) where first presentation at emergency services led to faster treatment initiation. It is suggested that emergency services were utilized more often by non-native-born groups because of the language barrier to usual mental health care services. Entering early intervention services through emergency services has previously been associated with poorer engagement (93). Although Singh and colleagues stated that there is no robust evidence for an association between cultural aspects and differences in pathways to care (94), the present study demonstrates a relation between immigration status and pathway to care. An earlier study by Morgan and colleagues did not find a relation between ethnicity and DUP (95;96). The difference between their study and the present one is that their definition of ethnicity was based on origin and not on immigration status (first or second). Differences in DUP might therefore be related to the effects of immigration and not to ethnic background.

Overall DUP in the highly urbanized area is relatively short while patient delay is still relatively long. This could be explained by the fact that all second generation immigrants live in such an area which calls for specific interventions to improve detection of psychosis among first and second generation immigrants.

METHODOLICAL CONSIDERATIONS

DUP is a concept with several definitions and different measures which hampers the comparability of the results of different studies. The onset of psychosis is nearly always retrospectively determined and based on information from patients. This can lead to an information bias. In this study information from family members and medical files was also used which may have improved the reliability of our data (3). Although data was collected by different members of the research team, all cases were discussed in researchers meetings until consensus was reached which may have reduced observer bias.

Literature on the association between DUP and migration status is sparse. More research is needed on this subject. In our study all second generation immigrants lived in a highly urbanized area, in future research it is recommended to include also second generation immigrants who live in urban or rural area.

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DECLARATION OF INTEREST

The authors have not transmitted any conflict of interest.

REFERENCE LIST

(1) Addington J, Van Mastrigt S, Hutchinson J, Addington D. Pathways to care: help seeking behaviour in first episode psychosis. Acta Psychiatr Scand 2002; 106(5):358-364.

(2) Anderson KK, Fuhrer R, Malla AK. The pathways to mental health care of first-episode psychosis patients: a systematic review. Psychol Med 2010;1-13.

(3) Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 1992; 49(8):615-623.

(4) Bechard-Evans L, Schmitz N, Abadi S, Joober R, King S, Malla A. Determinants of help-seeking and system related components of delay in the treatment of first-episode psychosis. Schizophr Res 2007; 96(1-3):206-214.

(5) Boonstra N, Wunderink L, Sytema S, Wiersma D. Improving detection of first-episode psychosis by mental health-care services using a self-report questionnaire. Early Intervention in Psychiatry 2009;(3):280-296.

(6) Brunet K, Birchwood M, Lester H, Thornhill K. Delays in mental health services and duration of untreated psychosis. Psychiatric Bulletin 2007;(31):408-410.

(7) Compton MT. Barriers to initial outpatient treatment engagement following first hospitalization for a first episode of nonaffective psychosis: a descriptive case series. J Psychiatr Pract 2005; 11(1):62-69.

(8) Compton MT, Chien VH, Leiner AS, Goulding SM, Weiss PS. Mode of onset of psychosis and family involvement in help-seeking as determinants of duration of untreated psychosis. Soc Psychiatry Psychiatr Epidemiol 2008; 43(12):975-982.

(9) Harrison G, Holton A, Neilson D, Owens D, Boot D, Cooper J. Severe mental disorder in Afro-Caribbean patients: some social, demographic and service factors. Psychol Med 1989; 19(3):683-696.

(10) Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. Arch Gen Psychiatry 2005; 62(9):975-983.

(11) Morgan C, Abdul-Al R, Lappin JM, Jones P, Fearon P, Leese M et al. Clinical and social determinants of duration of untreated psychosis in the AESOP first-episode psychosis study. Br J Psychiatry 2006; 189:446-452.

(12) Morgan C, Fearon P, Hutchinson G, McKenzie K, Lappin JM, Abdul-Al R et al. Duration of untreated psychosis and ethnicity in the AESOP first-onset psychosis study. Psychol Med 2006; 36(2):239-247.

(13) Morgan C, Mallett R, Hutchinson G, Bagalkote H, Morgan K, Fearon P et al. Pathways to care and ethnicity. 2: Source of referral and help-seeking. Report from the AESOP study. Br J Psychiatry 2005; 186:290-296.

(14) Nelson B, Yung AR. When things are not as they seem: detecting first-episode psychosis upon referral to ultra high risk ('prodromal') clinics. Early Intervention Psychiatry 2007;(1):208-211.

(15) Nienhuis FJ, van de WG, Rijnders CA, de Jonge P, Wiersma D. Validity of a short clinical interview for psychiatric diagnosis: the mini-SCAN. Br J Psychiatry 2010; 196(1):64-68.

(16) Nishii H, Yamazawa R, Shimodera S, Suzuki M, Hasegawa T, Mizuno M. Clinical and social determinants of a longer duration of untreated psychosis of schizophrenia in a Japanese population. Early Interv Psychiatry 2010; 4(2):182-188.

(17) Norman RM, Lewis SW, Marshall M. Duration of untreated psychosis and its relationship to clinical outcome. Br J Psychiatry Suppl 2005; 48:s19-s23.

(18) Norman RM, Malla AK, Verdi MB, Hassall LD, Fazekas C. Understanding delay in treatment for first-episode psychosis. Psychol Med 2004; 34(2):255-266.

(19) Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry 2005; 162(10):1785-1804.

(20) Rietdijk J, Dragt S, Klaassen R, Ising H, Nieman D, Wunderink L et al. A single blind randomized controlled trial of cognitive behavioural therapy in a help-seeking population with an At Risk Mental State for psychosis: the Dutch Early Detection and Intervention Evaluation (EDIE-NL) trial. Trials 2010; 11:30.

(21) Selten JP, Veen N, Feller W, Blom JD, Schols D, Camoenie W et al. Incidence of psychotic disorders in immigrant groups to The Netherlands. Br J Psychiatry 2001; 178:367-372.

(22) Singh SP. Outcome measures in early psychosis; relevance of duration of untreated psychosis. Br J Psychiatry Suppl 2007; 50:s58-s63.

(23) Singh SP, Cooper JE, Fisher HL, Tarrant CJ, Lloyd T, Banjo J et al. Determining the chronology and components of psychosis onset: The Nottingham Onset Sche-

dule (NOS). Schizophr Res 2005; 80(1):117-130.

(24) Singh SP, Grange T. Measuring pathways to care in first-episode psychosis: a systematic review. Schizophr Res 2006; 81(1):75-82.

(25) Snowden LR, Yamada AM. Cultural differences in access to care. Annu Rev Clin Psychol 2005; 1:143-166.

(26) Wolff G, Pathare S, Craig T, Leff J. Community knowledge of mental illness and reaction to mentally ill people. Br J Psychiatry 1996; 168(2):191-198.

(27) Wunderink L, Nienhuis FJ, Sytema S, Wiersma D. Predictive validity of proposed remission criteria in first-episode schizophrenic patients responding to antipsychotics. Schizophr Bull 2007; 33(3):792-796.

(28) Yamazawa R, Mizuno M, Nemoto T, Miura Y, Murakami M, Kashima H. Duration of untreated psychosis and pathways to psychiatric services in first-episode schizophrenia. Psychiatry Clin Neurosci 2004; 58(1):76-81.

CHAPTER 6

Improving detection of first episode psychosis by mental health care services using a self-report questionnaire

Running head:
Improving detection of psychosis

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ABSTRACT

OBJECTIVE

To examine the utility of the Community Assessment of Psychic Experiences (CAPE)-42, a self-report questionnaire, to improve detection of first episode psychosis in new referrals to mental health services.

METHOD

At first contact with mental health care services patients were asked to complete the CAPE-42 and were then routinely diagnosed by a clinician. Standard diagnoses were obtained by means of the mini-SCAN.

RESULTS

Of 246 included patients, 26 (10.6%) were diagnosed with psychosis according to the mini-SCAN. Only 10 of them were recognized by clinical routine, and 16 psychotic patients were not properly identified. Using an optimal cut-off of 50 on the frequency or distress dimension of the positive subscale of the CAPE-42 detected 14 of these misdiagnosed patients. The sensitivity of the CAPE-42 at this cut-off point was 77.5 and the specificity 70.5.

CONCLUSION

Systematic screening of patients using a self-report questionnaire for psychotic symptoms improves routine detection of psychotic patients when they first come into contact with mental health services.

Keywords: early detection; schizophrenia; early intervention, duration of untreated psychosis.

INTRODUCTION

Early treatment in first episode psychosis is one of the few available points of intervention to improve prognosis. Duration of untreated psychosis (DUP) is defined as the time interval between the onset of the first psychotic symptoms and initiation of adequate treatment (1). Short DUP has been associated with an earlier and better level of remission (2-4), a better chance of recovery (5), lower relapse rates (6;7), less cognitive deterioration (8), less positive (9-12) and negative symptoms (3;13), and better social functioning (14;15). The results of these studies are not directly comparable because of differences in adjusting to conceivable determinants of DUP, measurement of outcome variables and the fact that the definition of DUP has been operationalized differently. Despite these difficulties in comparing of results, all evidence points in the same direction: a longer DUP is associated with poorer outcomes. DUP seems to be an independent predictor of illness and treatment outcome (16), though the causal nature of this relationship has yet to be established. The most important hypothesis explaining the deleterious effects of a longer DUP is that emergent and active psychosis causes progressive gray matter loss, mainly during the critical period around the first episode (17;18).

An important prerequisite for early treatment is early detection. Over the past ten years specific programs for early detection and treatment of first episode psychosis have been developed with the aim of reducing DUP. These programs – which are probably worthwhile even though there is no firm evidence to support their efficacy (19) - are primarily focused on reducing delay in help-seeking and delay in referral to health services. For example the Scandinavian TIPS study revealed that intensive education of the general public, schools and the primary health care services to help them recognize psychotic symptoms was the key to reducing delay in help seeking and delay in referral by primary care (20;21). Norman et al. describe two components representing DUP; firstly the delay caused by the patients contacting health professionals and secondly the delay caused by services after the first contact has already been made (1). Both of these delay components appear to be of equal importance. Patients who had their first contact with services before the first onset of psychosis had a substantial longer service delay component. This also holds true for those patients who had their first contact around their first onset of psychosis (1). Brunet et al. (22) even describe three components of DUP as: delay in help-seeking, delay in referral and delay in recognition by mental health care services. The delay caused by mental health services was found to account for 35% of overall DUP in a study of 80 participants from the inner city of Birmingham (22). Both Norman et al. and Brunet et al. argue that efforts to minimize effects of DUP should be primarily targeted at a reduction of the service delay. Very recently, a large scale multi-centre study of pathways to care also demonstrated that a substantial proportion of DUP was caused by delay after first contact by mental health care services (23). The evidence suggests that mental health care services do not properly recognize psy-

chosis. We hypothesized 1) that a significant number of patients with a first episode psychosis who are newly referred to mental health care services are not recognized by routine clinical procedures and 2) that use of a self-report questionnaire CAPE-42 will improve recognition of first episode psychosis.

MATERIAL AND METHODS

SUBJECTS

Patients with a first-ever contact with mental health care services in part of the Dutch province of Friesland (catchment area of 300.000 inhabitants) during a period of 18 months (November 2006 - April 2008) were considered for inclusion in the present study. Patients were excluded if they (1) were not between the ages of 18 and 65, (2) were unable to understand and/or speak Dutch, (3) were mentally retarded, (4) did not enter treatment within two months or (5) were clinically diagnosed with a DSM-IV V-code for psychosocial problems. The characteristics of the sample are shown in table 1. During the selected inclusion period of 18 months 1,329 first contact patients were referred to mental health care services. Of them, 372 did not meet inclusion criteria: 7 patients were unable to speak Dutch, 7 patients were excluded because of mental retardation, 23 patients were younger than 18 or older than 65, 257 did not enter treatment after their first visit and therefore no information was collected and 78 patients were clinically diagnosed with a DSM-IV V-code for psychosocial problems only. A random sample of 350 patients was drawn from the 957 patients who met inclusion criteria, and they were invited to participate in the study and provided informed consent. Data for 104 patients were incomplete: clinical diagnoses of 27 patients were not reported, 40 patients did not complete the CAPE-42 (24) and 37 patients refused to be interviewed with the mini-SCAN (25). 246 patients (70%) had complete data. These patients did not differ significantly on gender, age or baseline GAF scores from the total eligible population of 957 patients or from the 104 patients from whom data were incomplete.

ASSESSMENT

Figure 1 shows the consort flow chart. Patients were asked to complete the self report questionnaire Community Assessment of Psychic Experiences (CAPE)-42 (24). In addition to the clinical diagnostic routine outlined by the DSM-IV (26), patients were diagnostically assessed by a research-psychiatrist or psychologist using the mini-Schedule for Clinical Assessment in Neuropsychiatry (mini-SCAN). We selected this instrument as the ‘gold standard’ for diagnosis (25). Blinding procedures were put in place for all assessments. Clinicians were blinded from mini-SCAN results, researchers were kept blind from clinicians’ diagnoses. Both clinicians and researchers were kept blind from CAPE-42 results.

INSTRUMENTS

THE CAPE-42

The Community Assessment of Psychic Experiences (CAPE)-42 is a 42 item self-report questionnaire measuring positive and negative psychotic symptoms and depressive symptoms on a two dimensional scale. The first dimension measures the frequency of symptoms on a four point scale of 'never' = 1, 'sometimes' = 2, 'often' = 3 and 'nearly always' = 4, and the second dimension measures the degree of distress caused by the experience: 'not distressed' = 1, 'a bit distressed' = 2, 'quite distressed' = 3 and 'very distressed' = 4. The total score ranges from 42 to 168 on both dimensions. The positive subscale counts 20 items (range 20 -80 on both dimensions), the negative subscale 14 items (range 14 – 56 on both dimensions) and the depressive subscale 8 items (range 8 – 32 on both dimensions) (24;27-29). The CAPE-42 has been designed to assess lifetime psychotic experiences in the general population.

MINI-SCAN

Patients were diagnostically assessed with the mini-SCAN, a short version of the validated Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1) using the same algorithm (30). The mini-SCAN was used as the 'gold standard' for diagnosis in the present study to assess the sensitivity and specificity of the CAPE-42. Like its predecessor the mini-SCAN is a semi-structured diagnostic interview used to establish an axis-1 DSM-IV diagnosis (26). The mini-SCAN has an advantage in offering a more uniformly defined interactive computerized interviewing schedule and a brief time of administration of thirty to sixty minutes.

TRAINING AND RELIABILITY

The diagnostic mini-SCAN interviews were administered by research-psychiatrists and psychologists who are familiar with psychopathology classification systems and were formally trained by the Dutch WHO Centre for Training and Research at the University Medical Center Groningen, Department of Psychiatry. Interviewers were trained in administration techniques and software operating instructions of the software program. Reliability was enhanced by rating videotaped interviews, followed by group reviews of the ratings. Inter-rater reliability for the mini-SCAN was established by a pairwise comparison of 3 raters, all rating the same 15 randomly selected subjects. The mean of the pairwise comparison unweighted kappa score on the diagnostic category appeared to be high (kappa= .87).

STATISTICAL ANALYSIS

We used receiver operator characteristics (ROC) to calculate the maximum AUC defining the best scale and the optimal cut off level on that scale of CAPE-42. The AUC ranges from 0.5 (the discriminatory ability of a test is no better than chance) to 1.0 (perfect discriminatory ability). SPSS (version 15.0; SPSS Inc. Chicago, Illinois, USA) was used to analyze the data.

RESULTS

PATIENT SAMPLE

26 (11%) of the 246 included patients had a psychotic disorder according to the mini-SCAN. 73% of them were males (n=19) with a mean age of 33.7 years (SD= 12.6); women had a mean age of 38.4 years (SD= 13.5). Only 10 of these 26 patients were diagnosed with a psychotic disorder by the clinician, the other 16 patients were assigned to other diagnoses: mood disorder (n=7), anxiety disorder (n=1), adjustment disorder (n=5), substance related disorder (n=2) and impulse control disorder (n=1). An overview of mini-SCAN diagnoses versus clinical diagnosis is shown in table 2. Patients detected as having a psychotic disorder by the mini-SCAN did not significantly differ from the undetected patients on gender, age or baseline GAF scores. Using mini-SCAN as the 'gold standard' for psychiatric diagnosis of psychosis, ROC analyses were conducted on the positive symptom subscale scores from the frequency and distress dimensions of the CAPE-42 (Figure 2). The AUC score for the positive subscale from the frequency dimension was .76 and the AUC for the positive subscale from the distress dimension was .66 (p<.001).

Figure 1. Flow chart

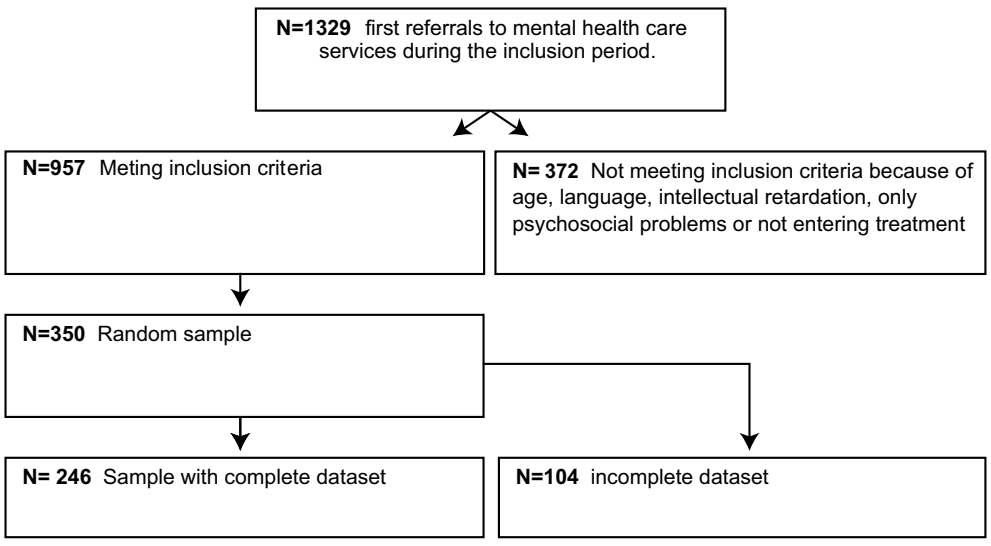

Figure 2. Receiver operator characteristic (ROC) curve for Community Assessment of Psychic Experiences (CAPE) positive subscale frequency and distress dimensions for the mini-Schedule for Clinical Assessment in Neuropsychiatry psychosis. Diagonal segments are produced by ties.

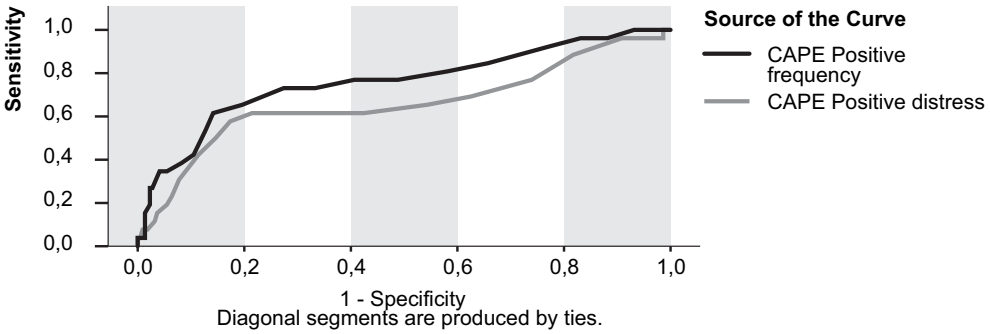

Table 1. Patient characteristics (n=246)

	N mean (SD)	(%)
Gender		
Male	118	(48.0)
Female	128	(52.0)
Age (mean ± SD)	37.5	(12.7)
Male (mean ± SD)	37.6	(12.2)
Female (mean ± SD)	37.3	(12.2)
GAF baseline score (mean ± SD)	60.3	(8.4)
Employment		
Yes	148	(60.2)
No	95	(38.6)
Unknown	3	(1.2)
Working hours/ week (mean ± SD)	148	27.9 (14.0)
Living situation		
Living with a partner/ family	115	(46.7)
Living alone	130	(52.8)
Unknown	1	(0.4)

Table 2. Diagnostic distribution; mini-SCAN diagnosis of psychosis versus clinical diagnosis (n=26)

		Clinical diagnosis								
		Psychotic disorder				No psychotic disorder				
		295.9	297.1	298.8	298.9	mood disorder	substance induced disorder	adjust-ment disorder	anxiety disorder	impulse-control disorder
Mini-SCAN diagnosis	295	0	0	0	3	1	0	0	0	0
	297.1	0	2	0	0	0	0	0	0	0
	298.8	1	0	1	1	1	1	1	0	0
	298.9	0	0	1	1	5	1	4	1	1

Table 3. Different cut-off points on CAPE-42 positive subscale (n=246)

Cut off point on CAPE positive subscale frequency or distress dimension	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
41	100	5.9	11.2	100
43	96.2	16.4	12.0	97.3
45	84.6	33.6	13.1	94.9
48	76.9	57.3	17.5	95.5
50	76.9	70.5	23.5	96.3
52	65.4	84.1	32.7	95.4
54	42.3	87.7	28.9	92.8

PPV = positive predictive value **NPV** = negative predictive value

Table 4. Diagnostic partition of patients (n=246)

	Clinical diagnosis				
	Psychotic disorder		No psychotic disorder		
	mini-SCAN psychotic disorder	mini-SCAN no psychotic disorder	mini-SCAN psychotic disorder	mini-SCAN no psychotic disorder	**Total**
CAPE-42 score ≥ 50 on positive subscale frequency or distress dimension	6	0	14	65	**85**
CAPE-42 score < 50 on positive subscale frequency or distress dimension	4	0	2	155	**161**
Total	10	0	16	220	**246**

Since the aim of the present study was to improve detection of first episode psychotic patients with a self report questionnaire, sensitivity should be maximized, with as few false positives as possible. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the CAPE positive subscale frequency or distress dimension at various cut-off points are presented in table 3. A cut-off score of 50 on the CAPE-42 positive subscale of the frequency dimension or 50 on the positive subscale of the distress dimension with a sensitivity of 77% and a specificity of 70.5% appear to be optimal.

The proportion of patients with CAPE-42 scores above 50 on the positive subscale frequency or distress who are correctly diagnosed with a psychotic disorder (PPV) was 23.5% and the proportion of patients with negative CAPE-42 scores on the positive subscale frequency or distress who are correctly diagnosed as non psychotic (NPV) was 96%. Four of the six patients not detected by CAPE-42 with these cut-off scores were identified by clinical routine. Results are shown in table 4. The clinicians agreed to change the clinical diagnosis into the mini-SCAN diagnosis of a psychotic disorder for all 16 patients who were not properly clinically diagnosed with a psychosis initially.

DISCUSSION

We found that in routine clinical practice patients were not appropriately recognized leaving a substantial number of psychotic patients undetected. We showed that implementation of a self report questionnaire, the CAPE-42, improved recognition of first episode psychotic patients.

The finding that first episode psychotic patients are undetected is in accordance with recently published data reporting a delay in recognition and initiation of adequa-

te treatment of first episode psychotic patients caused by mental health services was reported (23). These findings consistently stress the importance of timely recognition of first episode psychotic patients by mental health care services. In the present study 16 psychotic patients (62% of all psychotic patients) were initially missed by the clinician. A first possible explanation might be that many psychotic patients do not present their psychotic symptoms overtly and clinicians do not thoroughly investigate the possibility of a psychosis as a routine procedure, e.g. in a differential diagnosis. In a recent study we found that about half of the patients presenting at least two specific psychotic symptoms were diagnosed with a non-psychotic disorder and did not receive adequate treatment in accordance with these psychotic symptoms (31). A second explanation might be the lack of revision of diagnostic categorization after diagnosis has once been set. This has also been suggested by Norman et al (1). Systematic initial screening and routine outcome assessment procedures during the course of treatment could help to prevent these flaws in clinical diagnosis. In the present study we used the CAPE-42 as a systematic initial screener. The next step is to define the most useful cut-off score: the lower the cut-off, the more patients will be detected, but the more diagnostic interviews will have to be done. We decided that a CAPE-42 cut-off score of 50 on positive subscale frequency or distress dimension as add on to clinical diagnosis was the optimal threshold to further screening with miniSCAN. But other policy makers could make other choices depending on their aims. E.g. lowering the cut-off score to 41 would include only two extra psychotic patients in our sample, at the expense of 148 extra mini-SCAN interviews (233 in stead of 85). At a CAPE-42 cut-off score of 50 on the positive subscale frequency or distress dimension, of 26 psychotic patients, 20 were detected. Of the remaining six patients four were clinically diagnosed with a psychotic disorder.

The six undetected patients all had relatively low scores on the positive dimension, and also lower scores on the negative subscale frequency and distress dimension compared to the 20 patients who were detected by CAPE-42. For the distress dimension this difference was significant (p=.007).

The two patients who remained undetected had higher scores on the negative subscale frequency and distress dimension, even though this difference is not significant. These patients might have been assigned to a diagnosis of non-psychotic disorder because of their more prominent negative symptoms and relative lack of positive symptoms.

The incidence of first episode psychosis is relatively low. As a result, relatively large samples of patients would have to be screened to identify new cases of psychosis. However the advantage of screening a population of new referrals with psychiatric problems is considerable; given the risk associated with long treatment delay, the investment seems to be a justified. This study demonstrates once again that the delay within mental health care services should not be underestimated. Psychotic patients appear to be seriously underdetected. More systematic efforts should be

invested in detecting psychotic patients at their first contacts with mental health care instead of emphasizing the importance of detecting psychotic patients hidden in the general population. Systematic screening by a self-report questionnaire, in addition to clinical diagnosis, seems to be an important tool to reduce the duration of untreated psychosis due to mental health care service delay. The CAPE-42 is a self report questionnaire and therefore based on subjective reports. The reliability of self reported psychotic symptoms can be disputed. However previous studies show that self report can be used to assess severity of psychosis in clinical and research settings (32). Moreover patients appear to be more willing to report psychotic symptoms and experiences using self-report questionnaires than in a personal interview (33). A possible limitation of this study is the exclusion of patients with only psychosocial problems, and of patients who were not accepted for treatment within two months which may also explain the relatively large proportion of psychotic patients in our sample (i.e. 26/246). We also included only patients who were able to speak and understand Dutch; findings are not representative for the non-Dutch speaking patients. However the proportion of non-Dutch speaking patients in the areas studied is very low.

It was shown recently by a number of studies that a significant proportion of psychotic patients remain undetected by mental health services. To the best of our knowledge this study is one of the first to examine systematic screening using a self-report questionnaire for psychotic symptoms that shows significant improvement in routine detection of psychotic patients at first contact with mental health services.

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DECLARATION OF INTEREST

None

REFERENCE LIST

(1) Norman RM, Malla AK, Verdi MB, Hassall LD, Fazekas C. Understanding delay in treatment for first-episode psychosis. Psychol Med 2004; 34(2):255-266.

(2) Malla AK, Norman RM, Manchanda R, Ahmed MR, Scholten D, Harricharan R et al. One year outcome in first episode psychosis: influence of DUP and other predictors. Schizophr Res 2002; 54(3):231-242.

(3) Simonsen E, Friis S, Haahr U, Johannessen JO, Larsen TK, Melle I et al. Clinical epidemiologic first-episode psychosis: 1-year outcome and predictors. Acta Psychiatr Scand 2007; 116(1):54-61.

(4) Wunderink A, Nienhuis FJ, Sytema S, Wiersma D. Treatment delay and response rate in first episode psychosis. Acta Psychiatr Scand 2006; 113(4):332-339.

(5) Wunderink L,Sytema S, Nienhuis FJ,Wiersma D. Clinical Recovery in First-Episode Psychosis . Schizophrenia Bulletin 2008; 10.1093/schbul/sbn143.

(6) Altamura AC, Bassetti R, Sassella F, Salvadori D, Mundo E. Duration of untreated psychosis as a predictor of outcome in first-episode schizophrenia: a retrospective study. Schizophr Res 2001; 52(1-2):29-36.

(7) de Haan L, Linszen DH, Lenior ME, de Win ED, Gorsira R. Duration of untreated psychosis and outcome of schizophrenia: delay in intensive psychosocial treatment versus delay in treatment with antipsychotic medication. Schizophr Bull 2003; 29(2):341-348.

(8) Amminger GP, Edwards J, Brewer WJ, Harrigan S, McGorry PD. Duration of untreated psychosis and cognitive deterioration in first-episode schizophrenia. Schizophr Res 2002; 54(3):223-230.

(9) Black K, Peters L, Rui Q, Milliken H, Whitehorn D, Kopala LC. Duration of untreated psychosis predicts treatment outcome in an early psychosis program. Schizophr Res 2001; 47(2-3):215-222.

(10) Bottlender R, Sato T, Jager M, Wegener U, Wittmann J, Strauss A et al. The impact of the duration of untreated psychosis prior to first psychiatric admission on the 15-year outcome in schizophrenia. Schizophr Res 2003; 62(1-2):37-44.

(11) Larsen TK, Friis S, Haahr U, Joa I, Johannessen JO, Melle I et al. Early detection and intervention in first-episode schizophrenia: a critical review. Acta Psychiatr Scand 2001; 103(5):323-334.

(12) Norman RM, Malla AK, Manchanda R. Early premorbid adjustment as a moderator of the impact of duration of untreated psychosis. Schizophr Res 2007; 95(1-3):111-114.

(13) Perkins D, Lieberman J, Gu H, Tohen M, McEvoy J, Green A et al. Predictors of antipsychotic treatment response in patients with first-episode schizophrenia, schizoaffective and schizophreniform disorders. Br J Psychiatry 2004; 185:18-24.

(14) Drake RJ, Haley CJ, Akhtar S, Lewis SW. Causes and consequences of duration of untreated psychosis in schizophrenia. Br J Psychiatry 2000; 177:511-515.

(15) Harris MG, Henry LP, Harrigan SM, Purcell R, Schwartz OS, Farrelly SE et al. The relationship between duration of untreated psychosis and outcome: an eight-year prospective study. Schizophr Res 2005; 79(1):85-93.

(16) Norman RM, Lewis SW, Marshall M. Duration of untreated psychosis and its relationship to clinical outcome. Br J Psychiatry Suppl 2005; 48:s19-s23.

(17) DeLisi LE. The concept of progressive brain change in schizophrenia: implications for understanding schizophrenia. Schizophr Bull 2008; 34(2):312-321.

(18) Wood SJ, Pantelis C, Velakoulis D, Yucel M, Fornito A, McGorry PD. Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. Schizophr Bull 2008; 34(2):322-329.

(19) Marshall M, Rathbone J. Early intervention for psychosis. Cochrane Database Syst Rev 2006;(4):CD004718.

(20) Joa I, Johannessen JO, Auestad B, Friis S, McGlashan T, Melle I et al. The key to reducing duration of untreated first psychosis: information campaigns. Schizophr Bull 2008; 34(3):466-472.

(21) Johannessen JO, McGlashan TH, Larsen TK, Horneland M, Joa I, Mardal S et al. Early detection strategies for untreated first-episode psychosis. Schizophr Res 2001; 51(1):39-46.

(22) Brunet K. Birchwood M, Lester H, Thornhill K. Delays in mental health services and duration of untreated psychosis. Psychiatric Bulletin 2007; 31:408-410.

(23) Marshall M, Husain N, Warwurton J, Birchwood M, Lester H, Fowlr D, Sharma V, Jones P, Amos T, Lewis S. Delays in the pathway to care for a first episode of psychosis: an analysis of the components of duration of untreated psychosis from the Nation Eden Study. Early intervention in psychiatry 2008; 2 (suppl.1):A18.

(24) Stefanis NC, Hanssen M, Smirnis NK, Avramopoulos DA, Evdokimidis IK, Stefanis CN et al. Evidence that three dimensions of psychosis have a distribution in the general population. Psychol Med 2002; 32(2):347-358.

(25) Nienhuis FJ, Giel R. mini- Schedules for Clinical Assessment in Neuropsychiatry. Harcourt, 2000.

(26) Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association. Am J Psychiatry 1997; 154(4 Suppl):1-63.

(27) Hanssen M, Peeters F, Krabbendam L, Radstake S, Verdoux H, Van Os J. How psychotic are individuals with non-psychotic disorders? Soc Psychiatry Psychiatr Epidemiol 2003; 38(3):149-154.

(28) Hanssen MS, Bijl RV, Vollebergh W, Van Os J. Self-reported psychotic experiences in the general population: a valid screening tool for DSM-III-R psychotic disorders? Acta Psychiatr Scand 2003; 107(5):369-377.

(29) Konings M, Bak M, Hanssen M, Van Os J, Krabbendam L. Validity and reliability of the CAPE: a self-report instrument for the measurement of psychotic experiences in the general population. Acta Psychiatr Scand 2006; 114(1):55-61.

(30) Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R et al. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry 1990; 47(6):589-593.

(31) Boonstra N, Wunderink L, Sytema S, Wiersma D. Detection of psychosis by mental health care services; a naturalistic cohort study. Clin Pract Epidemol Ment Health 2008; 4:29.

(32) Niv N, Cohen AN, Mintz J, Ventura J, Young AS. The validity of using patient self-report to assess psychotic symptoms in schizophrenia. Schizophr Res 2007; 90(1-3):245-250.

(33) Hamera EK, Schneider JK, Potocky M, Casebeer MA. Validity of self-administered symptom scales in clients with schizophrenia and schizoaffective disorders. Schizophr Res 1996; 19(2-3):213-219.

CHAPTER 7

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

In this thesis we contrasted several aspects of the impact of delays in the treatment of psychosis with its early detection. We found that a delay in treatment is associated with a worse outcome.

The study reported above concerns new referrals to mental health care in two geographical areas in the Netherlands (Twente and Friesland). We found that in 3.7% of the cases primary psychotic symptoms, like delusions, hallucinations, disorganized speech and grossly disorganized behaviour were documented in the medical files. But of these only 37% of patients were diagnosed as suffering from a psychotic disorder and subsequently treated. The incidence of these psychotic disorders is about 22 per 100.000 inhabitants which is consistent with the 75th percentile of the cumulative incidence of a large recent meta-analysis (1).

Psychotic disorders are generally associated with poor outcome. An important factor in this association is the period of untreated psychosis. Early detection teams are aimed to shorten the untreated psychosis in order to achieve better functional outcome. We showed the usefulness of broadening the focus of early detection to negative symptoms. The relationship between duration of untreated psychosis (DUP) and negative symptoms is strong and persistent, even after 8 years of follow-up, and so far has been underestimated. Negative symptoms are difficult to treat and therefore prevention seems the best option of ameliorating the course of psychotic disorders. These negative symptoms are characterized by a decrease or complete loss of the ability to emotionally respond (blunted affect, affective flattening), a poverty of speech (alogia) and a lack of initiative (avolition, social withdrawal).

A DUP of less than 9 months appears to be a strong predictor of improvement of negative symptoms, while those symptoms are persistent in most patients with a DUP longer than 9 months. On average 30% of all new patients have a treatment delay of more than nine months. Mental health care services (MHS) are responsible for a substantial amount (i.e. 30%) of the overall DUP. Our study demonstrates that patient delay accounted for 60%, and referral delay for 10% of the total period of treatment delay.

Finally, we examined the usefulness of systematic screening by mental health care services. We found that implementation of systematic screening by a self-report questionnaire, i.e. the Community Assessment of Psychic Experiences (CAPE), significantly improved the recognition of first episode psychotic patients: 88% of non-detected patients would have been detected by the use of the CAPE.

In this chapter we will answer and discuss in more detail the main results of our studies with reference to the following questions:

1. How strong is the association between duration of untreated psychosis (DUP) and

negative symptoms at shorter and longer term?
2. To what extent is shortening the DUP still effective?
3. How can we shorten the DUP regarding referral and mental health care service delay?

THE ASSOCIATION BETWEEN DUP AND NEGATIVE SYMPTOMS

In our systematic review and meta-analysis we showed that DUP is not only associated with positive symptoms as described in two recent meta-analyses (2;3) but also with negative symptoms up to 8 years of follow-up. The relationship between a longer DUP and persistence of negative symptoms is consistent with the hypothesis that in many cases psychosis is a clinical manifestation of a progressive pathological process. However, our analysis does not prove that shortening DUP will benefit patients as the causality of the relationship still remains unclear. We have been unable to establish unequivocally that the presence of negative symptoms is a consequence of treatment delay. The most reliable way to demonstrate this satisfactorily is an experimental, randomized controlled parallel trial of the effect of shortening treatment delay (4). The best study so far is the Scandinavian TIPS study with a quasi-experimental (non- randomized) design that demonstrated that shortening DUP led to less severe negative symptoms up to 5 years of follow-up (5). These results suggest a cause-effect relationship. Although causality has not formally been established, numerous investigations have shown a consistent pattern confirmed by our meta- analysis: a longer DUP is associated with a worse outcome.

We now note that our results may suffer from a possible selection bias. The longer the follow-up the more healthy patients will be recovered and the more patients with persistent negative symptoms will be oversampled. A further limitation is the lack of information on the duration of negative symptoms prior to the emergence of positive symptoms and to the onset of the clinical syndrome of psychosis. Studies on the course of psychosis have shown that negative symptoms often precede positive psychotic symptoms (6). The presence and duration of negative symptoms at the time of the onset of psychosis may be predictors for treatment delay and thereby for treatment outcome. There is a certain degree of reciprocity. Patients with social withdrawal and flattening affect, for example, may have an insidious mode of onset whereby it is unclear which factor is responsible for poor prognosis. Flattening affect is also seen as a trait instead of a symptom and seems to be linked to underlying pathological processes involved in the development of treatment refractoriness (7). Nevertheless, our study showed the clinical usefulness of a broader perspective than merely focusing on positive symptoms: improvements are found when negative symptoms are taken into account.

A certain group of psychotic patients do not have any negative symptoms at first admission. It may be that different groups of psychotic disorders and their prognosis are characterized by the presence of negative symptoms. In our meta-analysis we did not find any differences between the presence of negative symptoms and gender, while it is assumed that males experience negative symptoms more often (8).

DEFINING SHORT DUP

We have shown above that the association between DUP and several outcome measures, including negative symptoms, is persistent over time. But to what extent is shortening of DUP still effective and is it sensible to shorten DUP in all cases? Is a DUP of one month short enough and will a further shortening improve outcome? Or when is DUP too long, e.g. 2 year, would a shortening of DUP by 6 months to one year, have an effect? In our meta-analysis we found a clear curvilinear relationship between DUP and negative symptoms at shorter and longer term follow-up, thus demonstrating a critical period of 9 months. For patients with a treatment delay of less than 9 months every week makes a difference, so that the shorter the DUP, the better. The shortening of longer DUPs seems to be of a lesser importance, the difference in outcome of a DUP of 2 years compared to one year appears to be marginal. Two large studies from Australia (9) and the UK (10) are in accordance with our results. They found the same curvilinear association between treatment delay and outcome for data on total PANSS and with a follow-up of 3 months and 1 year respectively.

The foregoing implies that the maximum benefit of early intervention will be gained only by focusing on patients in the DUP range with a maximum of 9 months. International studies show an average median DUP of approximately 6 months, so there is still much to be gained (11;12). We found in our meta-analysis and also in the Dutch cohort (Friesland and Amsterdam) about 70% of patients having a DUP shorter than 9 months. For these patients it holds true that the shorter the DUP the better. For the remaining 30% the question arises as to how DUP can be reduced. In particular for the outliers with an extreme long DUP, shortening with a few months or years may probably not be so effective. It is also possible that this group of patients who seek help at a very late stage, has a different type of disorder with a more degenerative course. The latter make up at least a part of the 15 to 20% of patients with poor outcome which generally emerge in course studies (13;14). Early detection programs probably will not change the prognosis for these patients, though had they been detected within 9 months this might have changed their course.

By obtaining individual patient data, our systematic review substantially increased the amount of information available for analysis. Although 16 of 28 eligible studies were included in the review, data on 84% of the total number of patients in those studies were available for the analysis. We propose a critical period of treatment delay of 9 months. As DUP is a complex variable defined by different criteria and is always determined retrospectively, there is a certain degree of recall bias. The separation between sub-threshold and threshold psychotic symptoms is not perfectly clear. In particular, this problem may occur for patients experiencing negative symptoms due to the insidious onset of psychosis. This fundamental problem applies to any study on treatment delay and can only be reduced to a large degree by the use of a clear definition based on a validated instrument such as the Nottingham Onset Scale (15) as established for recovery and remission (16).

TREATMENT DELAY IN PATHWAYS TO CARE IN THE NETHERLANDS

The incidence of psychotic disorders in the Netherlands is about 22 per 100.000 inhabitants, in accordance with the 75th percentile of the cumulative incidence of a large recent meta-analysis (1). This figure is based on only including patients diagnosed with a psychotic disorder at baseline and after 30 months of follow-up. However, including patients with a psychotic disorder at baseline as well as after 30 months follow-up led to an incidence of 30 per 100.000 inhabitants. We therefore believe that the incidence rate of 22 is a lower bound.

In our study we found that psychotic symptoms are far more common than often recognized. Although we cannot conclude that all patients need treatment for these symptoms, their diversity should not be overlooked in a mental health care system aiming at improving diagnosis and implementing treatment plans. In the follow-up study we demonstrated that clinicians overlooked a psychotic disorder in 62% of the patients during the initial diagnostic phase, and thus leaving a substantial number of psychotic patients undetected and untreated. These results support the assumption (presented in chapter 2 and 3) that patients with psychotic symptoms are in many cases not treated properly.

An explanation for this lack of detection might be that clinicians focus on the first diagnosis without taking the differential diagnosis (in this case of psychosis) into account. Patients who enter the mental health service with anxiety problems, even if they are secondary to psychotic symptoms, are treated for an anxiety disorder. A similar observation was noted in the EDIE-NL trial (17), which focused on patients who are at risk for psychosis. It was found that several patients already treated for anxiety or depression were in fact psychotic. Diagnostic procedures appear to be rather superficial, often based solely on the experiences presented to and followed by clinicians who are averse to revise their initial diagnostic classification (18). Moreover, our study was aimed at the detection of newly referred first episode psychotic patients, but the lack of revision procedures once diagnosis has been set is a major issue when dealing with under-detection (18).

English and Canadian studies have shown that each of the different components of DUP (such as patient delay, referral delay and health care delay), accounted for an equal part of overall DUP (18;19). In our study, however, patient delay was responsible for 60%, referral delay for 10% and mental health care delay for 30% of total DUP.

Patient delay was the longest in highly urbanized areas, most probably due to a large population of first and second generation immigrants. Patients who had already been treated by mental health care had the longest mental health care delay. In rural areas, the referral delay appeared to be the longest. Interestingly first and second generation immigrants initially experience a low service delay as they tend to alert the emergency services to their psychotic problems. Unfortunately, their first

encounters with mental health services are often marred by a lack of trust in the authorities. We recommend as a matter of urgency that targeted interventions be focused on first and second generation immigrants and so on reducing the numbers of patients seeking the help of the emergency services.

Mental health service delay accounts for 30% of the overall DUP in line with other published studies (18;19). Our data strongly argue for the use of a systematic screening of patients entering mental health services, making use of a procedure such as the CAPE. The implementation of the Community Assessment of Psychic Experiences (CAPE, (20)), a self-report questionnaire with which the presence and the experienced distress of psychic experiences can be mapped, provides a clear improvement in the recognition of psychosis. 62% of patients with a psychotic disorder were not detected by the clinician, while 88% of them would have been detected with the help of the CAPE using an optimal cut off of 50 on the frequency or distress dimensions of the positive subscale. The incidence of first episode psychosis is relatively low (22/100,000 at risk). As a result, relatively large samples of people would have to be screened in order to identify a single new case of psychosis. With the CAPE a new psychotic patient is identified if 17 first referred patients complete the questionnaire with 3 subsequently undergoing a diagnostic interview. The CAPE utilizes a self-assessment questionnaire based on subjective reports. Previous studies show that a self-report can be used to assess the severity of psychosis in clinical and research settings (21). Moreover, patients appear to be more willing to report psychotic symptoms and experiences using self-report questionnaires than in a personal interview (22). The CAPE questionnaire takes only 5 minutes to fill out by a patient. The advantage of screening a population of new referrals with psychiatric problems is considerable, given the risk associated with long treatment delay. This investment seems to be justified.

Besides the CAPE a number of other screening instruments can be used. For instance, the Prodomal Questionnaire (PQ, (23)), a 92-item self-report screening measures prodromal and psychotic symptoms and takes about 10 minutes to complete. The PQ list focuses on psychotic symptoms, but also aims at detecting patients at risk of becoming psychotic in the short term (one year). Moreover, the PQ may also be used in a two-step screening procedure in mental health. The second step in this two-stage evaluation process is the use of a diagnostic interview. When a patient has a PQ score above the threshold of 18, a diagnostic interview using the first 4 items of the Comprehensive Assessment of At Risk Mental State (CAARMS, (24)) is needed to establish whether the patient has an at-risk mental state for psychosis. Patients with an at-risk mental state have psychotic- like experiences or a genetic liability, combined with a decline in social functioning. Recent analysis showed that the CAARMS identifies young people with an at-risk mental state as well as with a first episode psychosis to an adequate degree (25). As mentioned above, a large number of patients are treated for other conditions which are secondary to psychosis. The study of Nelson et al. (25) supports the idea that a systematic screening may

help to identify psychotic patients at an earlier stage and therefore play a role in reducing DUP. Recently, a short version of the PQ with 16 items with a cut-off of 6 has been shown to have a sensitivity of 97% and specificity of 67%. While there is only scant evidence that a combination of the PQ and the CAARMS detects first episode psychosis apart from the detection of patients with an at-risk mental state, the signs are promising. Moreover this combination is advantageous, as there is no evidence that the CAPE together with a diagnotic interview will detect patients with an at-risk mental state. It is important to distinguish clearly an at-risk mental state and a first episode psychosis. Only 6.4% of patients with an at-risk mental state eventually develop a psychosis. Recent studies have failed to prove that the prescription of antipsychotics prior to the first episode is effective (26). The side effects of antipsychotic medication cannot be ignored and therefore psychosocial interventions like cognitive behaviour therapy, psycho-education and family interventions are the interventions of choice during the prodromal phase.

CLINICAL IMPLICATIONS

Psychosocial treatments for negative symptoms lack a substantial supportive evidence base, although three small trials (peer support groups (27), music therapy (28) and body oriented psychosocial therapy (29)) have produced promising results. There is no established treatment for primary negative symptoms (30;31). Pharmacological treatments, such as with antipsychotics have only a marginal impact on negative symptom severity (32). The lack of effective treatments for negative symptoms supports the effort of reducing DUP as an important clinical option. Currently, early intervention services focus primarily on the presence of positive symptoms. However, in view of the knowledge that negative symptoms have a strong influence on DUP and outcome, early intervention teams should be encouraged to focus also on the negative symptom complex of affective flattening, alogia (poverty of speech) and avolition (social withdrawal). The clinical classification of patients does not by itself answer their problems. We advocate that attention should also be paid to detecting patients who are socially excluded.

The association between DUP and outcome has been shown to be curvilinear. The shorter the treatment delay, the better the prognosis, up to a delay of 9 months. This supports the idea of early detection and intervention. Early intervention will probably not change the outcome for patients with a long DUP of several years. This argues in favour of informing first episode psychotic patients and their families clearly about the long term prognosis. In addition, patients can be assigned to the program of care and treatment most appropriately according to the stage of the disease they are in. The staging framework allows clinicians to select treatments relevant to the earlier stages of an illness, and to evaluate their effectiveness in preventing progression and producing remission or return to milder or earlier stages of disorder (33).

We believe that mental health professionals should be made more aware of the problem of undetected psychosis. One might expect a patient to be diagnosed and

treated for those symptoms lying at the core of the disease, regardless of the subjective complaints brought to the fore. Consortia of institutes for education of psychiatrists, psychologists and nurses and residency training should consider playing a more specific role in the process of awareness and recognition of psychotic experiences.

An international trend is now a shift towards the early identification of patients with an at-risk mental state for psychosis. An intervention at an earlier stage may prevent the development of a worse mental state. This opens the opportunity for shortening treatment delay when a transition to psychosis does occur. The implementation of the PQ combined with the CAARMS seems to us an important step towards the early detection of at-risk patients and also of patients who already have a psychotic disorder. The efficiency of the identification process will improve many-fold if these questionnaires are implemented routinely in mental health care systems. A significant recent decline in social functioning is an important criterion for the identification of an at-risk mental state and establishing its presence can be used to avoid unnecessary treatment and monitoring of symptoms that do not cause any distress. The instruments should be embedded in a psychosis care program to be carried out routinely regardless of the preferences of the clinician. A care program can only be effective if all help-seeking patients in the age range of the at risk population (e.g. between 14 and 35 years) are systematically screened and monitored.

Routine outcome monitoring (ROM) in mental health care may play an important role in the diagnostic revision process. ROM is currently implemented on a large scale in the Netherlands and provides the yearly assessment of the functional status (satisfaction with care, symptom severity, level of functioning etc) of the patient. These data are stored in the patient's medical files and available for diagnostic and treatment (re)evaluation. Besides mental health services, professionals from GP practices or social care institutions also may play a part in reducing treatment delay. Referral delay appears to be substantial in urban areas in the Netherlands. The low incidence rate of psychosis means that GPs only make contact with a first episode psychotic patient only every 4 to 5 years. However, the introduction of the "Praktijk Ondersteuner Huisartsenzorg - GGZ (POH-GGZ)", specialized psychiatric nurses in the GP practice, may improve the detection rate and a reduction of referral delay.

Finally, patient treatment delay was substantial for first generation immigrants living in highly urbanized areas. Interventions focusing on this subgroup are already being rolled out in Amsterdam. Postcards with educational slogans in the social scene, posters at GP practices, police stations and schools, interviews with Imams, information on Surinam Caribbean radio and briefings at benefits agencies are examples of interventions of improving knowledge and recognition of psychosis. As described earlier these kinds of interventions were shown in the Scandinavian TIPS study to be effective only as long as they were ongoing. The question thus arises as to the effect these interventions will have on this specific subgroup.

FUTURE RESEARCH

We have shown here that short DUP is of great importance, the shorter the better. Intervention studies focusing on the reduction of patient and referral delay are promising as long as the intervention is appropriate and of a sufficient duration (34;34-36). In our sample, patient delay accounted for a very significant proportion of the overall DUP, especially for immigrant patients. Further research is needed to design a suitable intervention for shortening patient delay in this subgroup.

Although the referral delay in our sample was not particularly long, the implementation of GP-practice-support-workers in the Netherlands ("Praktijk Ondersteuner Huisartsenzorg - GGZ (POH-GGZ)"), might shorten referral delay in GP practices. Further research is needed to show whether this has in fact been accomplished. Mental health service delay accounted for a substantial part of the overall DUP. We suggest a systematic screening of all patients referred to MHS in order to shorten this delay. Future investigation has to show to what extent DUP can be shortened to under 9 months in patients with long DUP. Anyway, mental health care services should be made more aware of the delays caused by not recognizing first episode psychotic patients.

As early intervention services start considering also negative symptoms, this attention shift should be accompanied by further research into the effects and feasibility of early detection and intervention on these symptoms in the course of psychotic disorders, including the prodromal phase.Future research should include determinants such as social disability and cognitive functioning and furthermore should delve deeper into their interdependence. Unfortunately we were prevented from undertaking this task in our meta-analysis due to the poor availability of such variables.

REFERENCE LIST

(1) McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med 2004; 2:13.

(2) Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. Arch Gen Psychiatry 2005; 62(9):975-983.

(3) Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry 2005; 162(10):1785-1804.

(4) Drake RJ, Lewis SW. Early detection of schizophrenia. Curr Opin Psychiatry 2005; 18(2):147-150.

(5) Larsen TK, Melle I, Auestad B, Haahr U, Joa I, Johannessen JO et al. Early detection of psychosis: positive effects on 5-year outcome. Psychol Med 2010;1-9.

(6) Hafner H. Onset and early course as determinants of the further course of schizophrenia. Acta Psychiatr Scand Suppl 2000;(407):44-48.

(7) Malla AK, Norman RM, Takhar J, Manchanda R, Townsend L, Scholten D et al. Can patients at risk for persistent negative symptoms be identified during their first episode of psychosis? J Nerv Ment Dis 2004; 192(7):455-463.

(8) Koster A, Lajer M, Lindhardt A, Rosenbaum B. Gender differences in first episode psychosis. Soc Psychiatry Psychiatr Epidemiol 2008; 43(12):940-946.

(9) Harrigan SM, McGorry PD, Krstev H. Does treatment delay in first-episode psychosis really matter? Psychol Med 2003; 33(1):97-110.

(10) Drake RJ, Haley CJ, Akhtar S, Lewis SW. Causes and consequences of duration of untreated psychosis in schizophrenia. Br J Psychiatry 2000; 177:511-515.

(11) Larsen TK, McGlashan TH, Moe LC. First-episode schizophrenia: I. Early course parameters. Schizophr Bull 1996; 22(2):241-256.

(12) Loebel AD, Lieberman JA, Alvir JM, Mayerhoff DI, Geisler SH, Szymanski SR. Duration of psychosis and outcome in first-episode schizophrenia. Am J Psychiatry 1992; 149(9):1183-1188.

(13) Wiersma D, Slooff CJ. Hoofdstuk 11 Epidemiologie en beloop. In: W.Cahn

LKIM-GRBLdHr, editor. Handboek Schizofrenie. De Tijdstroom,in druk., 2011.

(14) Menezes NM, Arenovich T, Zipursky RB. A systematic review of longitudinal outcome studies of first-episode psychosis. Psychol Med 2006; 36(10):1349-1362.

(15) Singh SP, Cooper JE, Fisher HL, Tarrant CJ, Lloyd T, Banjo J et al. Determining the chronology and components of psychosis onset: The Nottingham Onset Schedule (NOS). Schizophr Res 2005; 80(1):117-130.

(16) Andreasen NC. Standardized remission criteria in schizophrenia. Acta Psychiatr Scand 2006; 113(2):81.

(17) Gaag van der M. 2011.
Ref Type: Personal Communication

(18) Norman RM, Malla AK, Verdi MB, Hassall LD, Fazekas C. Understanding delay in treatment for first-episode psychosis. Psychol Med 2004; 34(2):255-266.

(19) Brunet K, Birchwood M, Lester H, Thornhill K. Delays in mental health services and duration of untreated psychosis. Psychiatric Bulletin 2007;(31):408-410.

(20) Konings M, Bak M, Hanssen M, van Os J, Krabbendam L. Validity and reliability of the CAPE: a self-report instrument for the measurement of psychotic experiences in the general population. Acta Psychiatr Scand 2006; 114(1):55-61.

(21) Niv N, Cohen AN, Mintz J, Ventura J, Young AS. The validity of using patient self-report to assess psychotic symptoms in schizophrenia. Schizophr Res 2007; 90(1-3):245-250.

(22) Hamera EK, Schneider JK, Potocky M, Casebeer MA. Validity of self-administered symptom scales in clients with schizophrenia and schizoaffective disorders. Schizophr Res 1996; 19(2-3):213-219.

(23) Loewy RL, Bearden CE, Johnson JK, Raine A, Cannon TD. The prodromal questionnaire (PQ): preliminary validation of a self-report screening measure for prodromal and psychotic syndromes. Schizophr Res 2005; 79(1):117-125.

(24) Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust N Z J Psychiatry 2005; 39(11-12):964-971.

(25) Nelson B, Yung AR. When things are not as they seem: detecting first-episode psychosis upon referral to ultra high risk ('prodromal') clinics. Early Intervention in Psychiatry 2007.

(26) de Koning MB, Bloemen OJ, van Amelsvoort TA, Becker HE, Nieman DH, van Der GM et al. Early intervention in patients at ultra high risk of psychosis: benefits and risks. Acta Psychiatr Scand 2009; 119(6):426-442.

(27) Castelein S, Bruggeman R, van Busschbach JT, van Der GM, Stant AD, Knegtering H et al. The effectiveness of peer support groups in psychosis: a randomized controlled trial. Acta Psychiatr Scand 2008; 118(1):64-72.

(28) Gold C, Solli HP, Kruger V, Lie SA. Dose-response relationship in music therapy for people with serious mental disorders: systematic review and meta-analysis. Clin Psychol Rev 2009; 29(3):193-207.

(29) Rohricht F, Priebe S. Effect of body-oriented psychological therapy on negative symptoms in schizophrenia: a randomized controlled trial. Psychol Med 2006; 36(5):669-678.

(30) Buckley PF, Stahl SM. Pharmacological treatment of negative symptoms of schizophrenia: therapeutic opportunity or cul-de-sac? Acta Psychiatr Scand 2007; 115(2):93-100.

(31) Kirkpatrick B, Fenton WS, Carpenter WT, Jr., Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull 2006; 32(2):214-219.

(32) Leucht S, Heres S, Kissling W, Davis JM. Evidence-based pharmacotherapy of schizophrenia. Int J Neuropsychopharmacol 2011;1-16.

(33) McGorry PD. Staging in neuropsychiatry: a heuristic model for understanding, prevention and treatment. Neurotox Res 2010; 18(3-4):244-255.

(34) Johannessen JO, McGlashan TH, Larsen TK, Horneland M, Joa I, Mardal S et al. Early detection strategies for untreated first-episode psychosis. Schizophr Res 2001; 51(1):39-46.

(35) Power P, Iacoponi E, Reynolds N, Fisher H, Russell M, Garety P et al. The Lambeth Early Onset Crisis Assessment Team Study: general practitioner education and access to an early detection team in first-episode psychosis. Br J Psychiatry Suppl 2007; 51:s133-s139.

(36) Tait L, Lester H, Birchwood M, Freemantle N, Wilson S. Design of the BiRmingham Early Detection In untREated psyChosis Trial (REDIRECT): cluster randomised controlled trial of general practitioner education in detection of first episode psychosis [ISRCTN87898421]. BMC Health Serv Res 2005; 5(1):19.

Samenvatting

Het proefschrift “Early detection of psychosis; why should we care?” beschrijft een aantal studies naar vroegtijdige detectie van patiënten met een eerste psychose. Lange tijd werd verondersteld dat een psychotische stoornis een ziekte is die gepaard gaat met ernstige onomkeerbare achteruitgang in sociaal functioneren. Huidige inzichten zijn optimistischer. Vroegtijdige (evidence based) behandeling blijkt een belangrijk gunstig effect te hebben op de prognose. Ondanks dat ze psychotische stoornissen rapporteren blijken patiënten hiervoor echter niet altijd adequate behandeling te krijgen. Zo bleek 63% van de groep patiënten met psychotische symptomen, zoals beschreven in de DSM-IV, hiervoor in 2 jaar niet behandeld te zijn.

In een meta-analyse toonden we aan dat de relatie tussen de onbehandelde psychoseduur en de prognose ook aanwezig is als het gaat om negatieve symptomen. Patiënten met een onbehandelde psychoseduur korter dan 9 maanden hebben minder ernstige negatieve symptomen op korte en lange termijn, waarbij tot 9 maanden geldt hoe korter hoe gunstiger. Aangezien er weinig interventies voor handen zijn om negatieve symptomen positief te beïnvloeden, lijkt het van belang om de duur van de onbehandelde psychose zo kort mogelijk te laten zijn. Ook al is niet vastgesteld dat het gaat om een causale relatie. Om te kunnen aantonen of er sprake is van causaliteit zou een gerandomiseerd gecontroleerd onderzoek gedaan moeten te worden, waarbij de ene groep een lange onbehandelde psychoseduur ondergaat en de andere groep een korte. Een dergelijke aanpak is uiteraard onethisch.

Er zijn verschillende factoren die van invloed zijn op de onbehandelde psychoseduur; de tijd die het duurt voordat de patiënt hulp zoekt; de tijd die het duurt om een psychose te herkennen en de patiënt door te verwijzen van de eerste naar de tweede lijn en de tijd die het kost om adequate behandeling in de tweede lijn te starten. Aangezien instellingen voor de geestelijke gezondheidszorg (GGZ) zijn gespecialiseerd in het vaststellen en behandelen van psychiatrische stoornissen, zou men mogen aannemen dat de duur van de onbehandelde psychose binnen de GGZ minimaal is. Wat echter blijkt is dat de GGZ verantwoordelijk is voor 30% van de totale vertraging. In onze studie werd aangetoond dat invoering van een self report vragenlijst aan de voordeur van de GGZ een relatief eenvoudige manier is om de detectie van psychotische patiënten te verbeteren. Intussen is deze methode ook reeds daadwerkelijk geïmplementeerd. Zo werden 16 van de 26 patiënten met een psychotische stoornis, die door de intakemedewerker niet als zodanig waren gemeld, met behulp van een self report vragenlijst, die slechts 10 minuten van de patiënt zijn tijd kost, wel herkend.

In hoofdstuk 1 wordt een algemene introductie gegeven over psychotische symptomen en psychotische stoornissen. Hierin worden incidentie en prevalentie cijfers besproken en daarnaast wordt het beloop van een psychotische stoornis vanuit his-

torisch perspectief belicht. De verschillende componenten die van invloed kunnen zijn op een vertraging, het belang van vroegtijdige behandeling en het komen tot een adequate behandeling worden eveneens in dit hoofdstuk behandeld.

De incidentie van niet affectieve psychotische stoornissen per geslacht in twee GGZ regio's in Nederland worden beschreven in hoofdstuk 2. In het onderzoek maakten we gebruik van de dossiers van alle patiënten tussen 18 en 45 jaar die in 2002 een eerste zorgcontact hadden bij GGZ Friesland of bij Mediant Twente. Dit betrof in totaal 6477 patiënten. Alle dossiers werden gescreend op vermelding van psychotische symptomen. Het doel van dit onderzoek was het vaststellen van het aantal niet-affectieve psychotische patiënten, waarbij onderscheid werd gemaakt naar geslacht en leeftijd. In de dossiers van 242 patiënten werden specifieke psychotische symptomen gerapporteerd. De diagnose werd aan het begin van het diagnostische proces geregistreerd en na 30 maanden werd de meest recente diagnose geregistreerd. Bij 75 patiënten was de diagnose op baseline alsook na 30 maanden een niet- affectieve psychotische stoornis. Deze patiënten werden gerekend tot de administratieve incidentie. Dit leverde een administratieve incidentie op van 2,2 (95% BI: 1,7-2,6) per 10.000 inwoners. Van de 75 patiënten waren er 49 man (65%). Dit betekent een incidentie voor mannen van 2,7 (95% BI; 2,1-3,4) en voor vrouwen van 1,6 (95% BI; 1,0-2,1) per 10.000 inwoners at risk. Het eerste zorgcontact met de geestelijke gezondheidszorg (GGZ) in verband met een niet-affectieve psychotische stoornis vond bij mannen op jongere leeftijd plaats dan bij vrouwen. De gemiddelde leeftijd voor mannen was bij 27,1 jaar (sd: 6,0), significant lager ($p < 0,003$) dan die voor vrouwen (29,6 jaar; sd: 8,7). Beide regio's verschilden niet significant van elkaar ($p > 0,2$). De gevonden incidentie komt overeen met de incidentie die in eerdere Nederlandse studies gevonden werd en ligt op het 75ste percentiel van de cumulatieve incidentie in een grote recente internationale review.

Internationale richtlijnen adviseren behandeling vanaf het eerste moment dat psychotische symptomen zich voordoen. De behandeling bestaat idealiter uit antipsychotica voor tenminste 2 jaar, in de dagelijkse praktijk worden deze richtlijnen niet altijd nageleefd. Het doel van het onderzoek zoals beschreven in hoofdstuk 3 was om vast te stellen in welke mate psychotische symptomen leiden tot een diagnose in het psychotische spectrum en in welke mate adequate behandeling wordt ingezet. De dossiers van alle patiënten tussen 18 en 45 jaar die in 2002 voor het eerst contact hadden met een GGZ instelling werden gescreend op gerapporteerde psychotische symptomen. In de dossiers van 242 (3,7%) werden specifieke psychotische symptomen gerapporteerd, te weten wanen, hallucinaties, onsamenhangende spraak en/ of ernstig chaotisch of katatoon gedrag. Van deze patiënten werd 37% gediagnosticeerd met een niet affectieve psychotische stoornis, 7% met andere psychotische stoornissen en 56% met een niet psychotische stoornis, of werden helemaal niet gediagnosticeerd. Ongeveer 90% van de patiënten met een psychotische stoornis kreeg antipsychotica voorgeschreven en ongeveer 50% van de patiënten bleef 2 jaar in zorg. De resultaten van dit onderzoek laten zien dat 63% van de 242 patiën-

ten met duidelijke psychotische symptomen na 2 jaar niet waren gediagnosticeerd en evenmin waren behandeld als zodanig. Dit kan betekenen dat er sprake is van een onderdetectie van psychotische stoornissen. Het verbeteren van het diagnostische proces aan de voordeur van de GGZ is naar ons idee dan ook de meest voor de hand liggende manier om vroegtijdige interventie bij psychotische stoornissen te bevorderen.

Vervolgens bekijken we in hoofdstuk 4 door middel van een meta-analyse, op basis van reeds verzameld materiaal, wat de relatie is tussen de onbehandelde psychoseduur en negatieve symptomen. Wetenschappelijke literatuur laat een relatie zien tussen de onbehandelde psychoseduur en andere uitkomstmaten zoals positieve symptomen, de kans op een relapse en de tijd tot remissie. Over de relatie tussen de onbehandelde psychoseduur en negatieve symptomen is nog weinig bekend, zeker niet over de relatie op lange termijn. In onze analyse is op basis van een systematische search gekeken naar studies die data beschreven over onbehandelde psychoseduur en negatieve symptomen. Daarbij zijn uit 402 onderzoeken 28 studies geselecteerd die voldeden aan de criteria De onderzoekers van deze 28 studies werden benaderd met het verzoek om hun data beschikbaar te stellen voor nadere analyse. Van de auteurs van 16 studies met een totaal van 3339 patiënten (84%) hebben we deze data ontvangen. De gemiddelde onbehandelde psychoseduur was 61.7 weken (sd=132,7) de mediaan was 12.0. Een kortere onbehandelde psychoseduur bleek significant gecorreleerd met minder ernstige negatieve symptomen, aan het begin van de ziekte, na 1 tot 2 jaar en na 5 tot 8 jaar. Een multilevel regressie analyse liet zien dat de relatie tussen negatieve symptomen en de onbehandelde psychoseduur niet lineair is. Mensen met een onbehandelde psychose van korter dan 9 maanden hadden een veel grotere kans op herstel van negatieve symptomen dan mensen met een onbehandelde psychoseduur van langer dan 9 maanden. Bij de onbehandelde psychoseduur korter dan 9 maanden gold: hoe korter hoe beter. In de TIPS studie, die is uitgevoerd in Scandinavië, werden soortgelijke resultaten gevonden. Daarin bleek dat, door middel van een interventie gericht op het sneller in zorg krijgen van patiënten, de onbehandelde psychoseduur en ook de ernst van de negatieve symptomen lager scoorden. Ondanks de TIPS studie en onze eigen resultaten kunnen we niet onomstotelijk aantonen dat er een causale relatie bestaat tussen de onbehandelde psychoseduur en negatieve symptomen. Aangezien er weinig evidence based interventies zijn om negatieve symptomen te kunnen beïnvloeden, lijkt een reductie van de onbehandelde psychoseduur een goede manier om deze symptomen te beïnvloeden.

Verschillende factoren dragen bij aan de onbehandelde psychoseduur; ten eerste vertraging in het zoeken naar hulp door de patiënt, ten tweede de vertraging als gevolg van het niet op tijd doorverwijzen van de eerste lijn naar de tweede lijn door bijvoorbeeld de huisarts en ten derde de vertraging als gevolg van het niet adequaat herkennen en behandelen door de GGZ. Aangezien de onbehandelde psychoseduur geassocieerd is met een slechtere prognose, is het van belang patiënten

zo snel mogelijk in behandeling te krijgen. Om de onbehandelde psychoseduur te kunnen verkorten is het belangrijk om te weten welke factoren deze componenten beïnvloeden.

In deze studie hebben we de invloed die migratie en urbaniciteit hebben op de onbehandelde psychoseduur bekeken en in hoofdstuk 5 beschreven. Daarvoor werd de onbehandelde psychoseduur vastgesteld van 182 patiënten met een eerste psychose uit rurale, stedelijke en zeer stedelijke gebieden door middel van de Nottingham Onset Schedule (NOS). Daarnaast hebben we de verwijzers van deze patiënten in kaart gebracht en de migratiestatus. Patiënten werden gecategoriseerd als autochtoon, 1e of 2e generatie immigrant. De gemiddelde DUP was 53,6 weken (SD=116,8). De vertraging als gevolg van het niet op tijd hulp zoeken door de patiënt was het langst voor patiënten die in zeer stedelijke gebieden wonen (Amsterdam), met name bij 2e generatie immigranten. De vertraging veroorzaakt door de GGZ was het langst voor patiënten bij wie de psychose begon op het moment dat ze al in behandeling waren van de GGZ, vermoedelijk als gevolg van een gebrek aan revisie van diagnostiek. Wij denken dat het belangrijk is dat er specifieke interventies komen gericht op patiënten die in zeer stedelijke gebieden leven met het doel de onbehandelde psychoseduur te verkorten. GGZ instellingen zouden de vroegtijdige herkenning aan de voordeur van de GGZ moeten verbeteren om de vertraging als gevolg van het niet herkennen en behandelen door GGZ instellingen te verminderen.

In hoofdstuk 6 brengen we in beeld hoe de implementatie van een selfreport vragenlijst, in dit geval de CAPE-42 (Community Assessment of Psychic Experiences), kan bijdragen aan de detectie van eerste psychose patiënten aan de voordeur van de GGZ. In een periode van 18 maanden hebben we alle patiënten die zich aanmeldden bij GGZ Friesland in de leeftijdcategorie 18-45 jaar gevraagd de CAPE-42 in te vullen. Blind van de CAPE-42 score werden patiënten gediagnosticeerd door de behandelaar. Van de kleine 1000 patiënten die aan de inclusiecriteria voldeden zijn ad random 350 patiënten uitgenodigd voor een klinisch interview met behulp van de mini-SCAN, een gevalideerd diagnostisch instrument om een diagnose op as 1 vast te stellen. Van 246 patiënten waren de data compleet. Van hen werden 26 patiënten (10,6%) gediagnosticeerd met een psychotische stoornis op basis van het interview met de mini-SCAN. Slechts 10 (38%) van hen waren ook als zodanig herkend door de behandelaar, de andere 16 (62%) patiënten waren niet herkend. Met een afkappunt van 50 op de frequentie en distress dimensie van de positieve subschaal van de CAPE-42 zouden 14 van de 16 die door de clinicus niet als zodanig waren herkend wel zijn gedetecteerd. De sensitiviteit behorende bij dit afkappunt is 77,5 en de specificiteit 70,5. Wij concluderen uit deze resultaten dat systematische screening door middel van een selfreport vragenlijst de detectie van psychotische patiënten aan de voordeur van de GGZ verbetert en we pleiten er dan ook voor dat hiervoor meer aandacht komt.

In hoofdstuk 7 worden de belangrijkste uitkomsten van de verrichte studies bespro-

ken, evenals de gevolgen van de gevonden resultaten voor de dagelijkse praktijk. De duur van de onbehandelde psychose wordt al langere tijd geassocieerd met een slechtere prognose. In dit proefschrift onderschrijven we deze waarneming. Vroege interventieteams hebben tot doel patiënten snel in zorg te krijgen, om op die manier de prognose van de patiënt positief te kunnen beïnvloeden. We hebben laten zien dat het nuttig kan zijn om niet alleen aandacht te hebben voor positieve symptomen maar ook voor negatieve symptomen, ook al tonen we met deze studie geen causaal verband aan tussen de onbehandelde psychoseduur en negatieve symptomen. Hiervoor zou een experimenteel, gerandomiseerd onderzoek gedaan moeten worden wat ethisch onhaalbaar is. De TIPS study in Scandinavië is een voorbeeld dat met zijn quasi experimentele design het beste in de buurt komt. In de TIPS study werd door middel van publiekscampagnes de onbehandelde psychoseduur verkort. Patiënten met een kortere onbehandelde psychoseduur bleken ook minder ernstige negatieve symptomen te hebben. Deze resultaten wijzen op een causaal verband, een patroon dat door onze meta- analyse ook wordt ondersteund. Het zou kunnen zijn dat er sprake is van een selectiebias, omdat gezonde patiënten vaker uit een onderzoek vallen omdat ze niet langer in behandeling zijn. Ook weten we niet hoe lang negatieve symptomen al aanwezig waren op het moment dat de positieve symptomen zich voordeden. De aanwezigheid en de duur van de negatieve symptomen ten tijde van de start van de psychose (positieve symptomen) zou bepalend kunnen zijn voor de onbehandelde psychoseduur. Mogelijk zoeken patiënten die al lange tijd negatieve symptomen hebben niet zo snel hulp, omdat ze zich al langere tijd hebben teruggetrokken uit het sociale leven.

Een onbehandelde psychoseduur korter dan 9 maanden blijkt een belangrijk criterium voor de prognose te zijn als het gaat om negatieve symptomen. Dit betekent dat het verkorten van de onbehandelde psychoseduur niet voor iedere patiënt effectief hoeft te zijn. Voor patiënten met een onbehandelde psychoseduur korter dan 9 maanden is iedere week korter van belang, maar voor patiënten met een onbehandelde psychoseduur van 5 jaar zal een jaar verkorten weinig effect opleveren. Dit zou betekenen dat het grootste belang ligt in het richten van de aandacht op patiënten die een onbehandelde psychoseduur hebben korter dan 9 maanden. Internationale studies laten een gemiddelde mediane DUP zien van 6 maanden. Ongeveer 30% van de patiënten heeft een onbehandelde psychoseduur van meer dan 9 maanden.

GGZ instellingen zijn verantwoordelijk voor een essentieel gedeelte van de totale onbehandelde psychoseduur, te weten ongeveer 30%. Een mogelijke verklaring is dat behandelaren zich richten op de eerste diagnose en deze over het algemeen niet aanpassen. De onderzoeken beschreven in dit proefschrift pleiten voor systematische screening aan de voordeur van de GGZ. Naast de CAPE-42, welke in het onderzoek is gebruikt dat is beschreven in hoofdstuk 6, wordt in Nederland in toenemende mate gebruik gemaakt van de prodromal questionnaire (PQ). Dat is een self report vragenlijst die naast de detectie van psychotische patiënten ook gericht is op de herkenning van patiënten met een verhoogd risico op het ontwikkelen van

een psychose. De PQ wordt altijd in een 2-traps procedure gebruikt. Wanneer een patiënt hoog scoort op de PQ, wordt door middel van een diagnostisch interview aan de hand van de Comprehensive Assessment of At Risk Mental State (CAARMS) vastgesteld of er inderdaad sprake is van een verhoogd risico op een psychose. Afhankelijk van de focus kan de CAPE in combinatie met een diagnostisch instrument of de PQ in combinatie met de CAARMS worden ingezet. Beide systemen zijn toereikend voor het doel van systematische screening aan de voordeur van de GGZ.

Aangezien, zoals door ons vastgesteld, de vertraging veroorzaakt door de GGZ 30% bedroeg, dient de revisie van diagnostiek ook systematisch te gebeuren. Dit past goed binnen routine outcome monitoring (ROM). De implementatie van de POH-GGZ in de huisartsenpraktijk zou de vertraging als gevolg van het niet op tijd verwijzen van de eerste lijn naar de tweede lijn kunnen verbeteren. Deze verpleegkundigen werken in meerdere huisartsenpraktijken en zijn veel meer ervaren in het herkennen van psychotische symptomen. In opleidingstrajecten dient hieraan, niet alleen bij de POH GGZ maar ook bij psychiaters, psychologen en verpleegkundigen uitgebreid aandacht besteed te worden.

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Het derde artikel van dit proefschrift beschrijft de meta analyse over de associatie tussen DUP en negatieve symptomen. Met dit artikel waarin geen eigen data is opgenomen ben ik het langste bezig geweest. Het was een grote klus om alle beschikbare data te kunnen gebruiken in één artikel. Bij het schrijven van dit artikel hebben Rianne Klaassen en Max Marshall een belangrijke rol gespeeld. Lieve Rianne, naast dat ik het heel leuk vind om samen met jou een artikel te schrijven heb ik veel van je geleerd. Het systematisch opbouwen van een wetenschappelijk artikel vonden we allebei lastig en ik denk dat we daarin van elkaar veel hebben geleerd. Ook de gesprekken over de kids heb ik als heerlijk relativerend ervaren. Ik hoop dat ik in de toekomst nog veel leuke dingen met je mag doen en wens je veel succes met de afronding van jouw proefschrift. Dear Max, thank you so much for your confidence in this article. I did not have enough focus in the stage in which I approached you. But you managed to lead me in the right direction. Thanks to your accuracy and sharpness I was able to raise the article to a higher level.

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Het laatste artikel van dit proefschrift beschrijft de duur van de onbehandelde psychose van de patiënten die behandeld worden door het VIP team in Friesland en Amsterdam. De NOS is afgenomen om de DUP te kunnen bepalen, het was soms lastig om ze ingevuld te krijgen maar het is gelukt. In Friesland wil ik Aaltsje Malda, Lianne Kampman, Greetje Duinstra, Ineke de Jong, Paula Puite, Menno Miedema, Elske van Gelderen, Leo van der Linden, Bouwe Post en ook Antien Nienhuis en Caroline Bruining bedanken voor hun inzet in deze. Last but not least wil ik Boudien van der Pol bedanken voor het opzoeken van alle ontbrekende gegevens, heerlijk dat je altijd vol goede moed aan de slag gaat. Met name dankzij jou is de data voor dit artikel representatief en dus bruikbaar. Beste VIPers, jullie zijn een geweldig team met veel expertise en het is super om met jullie samen te werken. Dit artikel heb ik geschreven met Bouke Sterk, ondanks het feit dat we slechts één keer face to face hebben gepraat over de opzet van het artikel hadden we de data en het artikel snel op orde. Bouke het was erg prettig samenwerken met je, wie weet komt er nog eens een herhaling. Lieuwe de Haan heeft ook in dit artikel en in de meta analyse een

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Publications and presentations

INTERNATIONAL PUBLICATIONS

Boonstra N, (2007) Statistiek in de sociale wetenschappen, Nederlandse bewerking van Howitt D., Cramer D., Pearson Prentice Hall NL, 3e druk.

Boonstra N, Wunderink L, Sytema S, Wiersma D, (2008) Detection of psychosis by mental health care services; a naturalistic cohort study, Clinical Practice and Epidemiology in Mental Health 2008, Dec 16, 4: 29.

Jenner J.A., Rutten S, Beuckens J, Boonstra N, Sytema S, Positive and useful auditory hallucinations: prevalence, characteristics, attributions and implications for treatment, Acta Psychiatrica Scandinavica, 118 30:238-45. Epub 2008 July 10.

Boonstra, N., Wunderink, L., Sytema, S., Wiersma, D., Improving detection of first-episode psychosis by mental health-care services using a self-report questionnaire. Early Intervention in Psychiatry, volume 3 Issue 4, Pages 289-295, 2009 November 18.

Boonstra N, Sterk, B, Wunderink W, Sytema S, De Haan L, Wiersma D, Association of treatment delay, migration and urbanicity in psychosis. European Psychiatry (2011), doi:10.1016/j.eurpsy.2011.05.001 (in press).

Boonstra N, Klaassen R, Sytema S, Marshall M, De Haan L, Wunderink L, Wiersma D. Duration of untreated psychosis and negative symptoms – a systematic review and meta- analysis of individual patient data. Submitted for publication.

NATIONAL PUBLICATIONS

Rutten S., Beuckens J., Boonstra N., Jenner J.A. (2007) Positieve en nuttige auditieve vocale hallucinaties, Tijdschrift voor Psychiatrie 49 11, 803-812.

Boonstra N, Wunderink L, de Wit PH, Noorthoorn E, Wiersma D. De administratieve incidentie van niet-affectieve psychosen in Friesland en Twente [The administrative incidence of non-affective psychoses in Friesland and Twente]. Tijdschrift voor Psychiatrie 2008;50(10):637-43.

ORAL AND POSTER PRESENTATIONS

2005

Boonstra, N., Detectie en geslachtsverdeling eerste psychose, waarom psychotische stoornissen bij vrouwen in eerste psychose moeilijk onderkend en behandeld worden. Congres Acute Psychiatrie, 7 oktober 2005, Lelystad.

2006

Boonstra, T.C., Wunderink, L., Incidence and gender distribution of non-affective psychotic disorders in the Netherlands. Schizophrenia Research Volume 86, Supplement 1, October 2006, Page S64 Abstract of the 5th International Conference on Early Psychosis Birmingham.

Boonstra, N., Mulder, P.J., Schizofreniezorg, een vak apart, SPV nascholing NVSPV, “Schizofrenie gezondheid en herstel”, 14-16 september 2006, Terschelling.

2007

Boonstra, N, Klaassen, R. Hoe krijgen we en houden we adolescenten met een eerste psychose in zorg? Schizofreniecongres, “zorg voor verband”, 22 november 2007, Zwolle.

Boonstra, N., Systematische detectie van eerste psychosen aan de voordeur van de GGZ; de rationale achter de EASEstudy. Symposium RGOc, Groningen, 5 november 2007.

Klaassen, R., Boonstra, N., Hoe krijgen en houden we adolescenten met een psychose in zorg? Congres GGZ Frysland ”It sil heve”, 22 februari 2007, Leeuwarden.

2008

Boonstra N, Wunderink L, Hamar S, Sytema S, Wiersma D., Improving detection of First Episode Psychosis: Self-Reported Positive Symptoms in First Contact with Mental Health Care, Schizophrenia Research 98 p.80, 2008.

Boonstra N, Wunderink L, Sytema S, Wiersma D, Improving Detection of First Episode Psychoses by Mental Health Care Services: the Results of First Contact Screening with a Self-Report Questionnaire, 1st Schizophrenia International Research Society Conference, Venice, Italy, June 21-25, 2008, Schizophrenia Research vol 102/1-3, Supp 2, p. 151, 2008

Boonstra, N, Malda A, Wunderink L, Klaassen R, Wiersma S, van der Tang, S., Detectie van Ultra High Risk Jongeren. Schizofreniecongres, “zorg voor kwaliteit”, 20 november 2008, Zwolle.

2009

Boonstra, N., Verhey, C., Castelein, S., Vroegdetectie en publiekscampagnes; een blijvend effect? Schizofreniecongres, “alledaags ongewoon” Zwolle 19 november 2009.

Boonstra, N., Gool, R., Mulder, P.J., Droes, J., Holleman, G., Verpleegkundige zorg is T.O.P. Schizofreniecongres, “alledaags ongewoon” Zwolle 19 november 2009.

Boonstra, N., Wunderink, L., Sytema, S., Wiersma, D., Improving detection of first episode psychosis by mental health care services: the results of first contact screening with a self-report questionnaire. Oral presentation. The 15th Biennial Winter Workshop in Psychoses, 15-18 November 2009, Barcelona.

2010

Boonstra, N. Zorg voor mensen met een eerste psychose! Congres zorg voor mensen met schizofrenie; as the World turns. 18 februari 2010, Ede.

Boonstra, N., Klaassen, R., Wunderink, L., Sytema, S., Wiersma, D., Duration of untreated psychosis and negative symptoms: how do they relate. Oral presentation, 2nd Schizophrenia International Research Society Conference, 10-14 April 2010, Firenze.

Wunderink, L., Sytema, S., Boonstra, N., Wiersma, D., DUP, Remission and Recovery in First Episode Psychosis, poster presentation, 2nd Schizophrenia International Research Society Conference, 10-14 April 2010, Firenze.

Boonstra, N., Wunderink, L., Sytema, S., Wiersma, D., Improving detection of first episode psychosis by mental health care services using a self report questionnaire, poster presentation, 2nd Schizophrenia International Research Society Conference, 10-14 April 2010, Firenze.

Boonstra, N., Slooff, C., Castelein, S., Parallelsymposium 'De nieuwe Richtlijn Schizofrenie', Schizofreniecongres Zorg in Beweging, Kenniscentrum Phrenos, 18 November 2010, Zwolle.

Boonstra, N., Klaassen, R., Wunderink, L., Sytema, S., Wiersma, D., The relationship between DUP and negative symptoms, a systematic review and analysis of individual patient data, poster presentation, 7th international conference on early psychosis, International Early Psychosis Association, 29 November- 1 December 2010, Amsterdam.

2011

Boonstra, N., Klaassen, R., Wunderink, L., Sytema, S., Wiersma, D., The relationship between DUP and negative symptoms, a systematic review and analysis of individual patient data, oral presentation, Voorjaarscongres, Amsterdam.

RGOC PUBLICATIONS INCLUDING DISSERTATIONS

Busschbach J.T. van, E. Visser, P. Bastiaansen, S. Sytema (2001). Hoe tevreden zijn huisartsen met de GGZ; Een enquête naar de samenwerking met de MFE in Zuidoost-Drenthe. RGOc-reeks, nummer 1, ISBN-10 90-367-1460-5

Jong de A. en P.M. van der Lubbe (2001). Groningse Vragenlijst over Sociaal Gedrag. Zelfbeoordelingsvragenlijsten voor het vaststellen van problemen in het interpersoonlijke functioneren. Handleiding. RGOc-reeks, nummer 2, ISBN-10 90-367-1463-X

Wiersma Durk, Jack A. Jenner, Fokko J. Nienhuis, Dennis Stant, Gerard van de Willige (2001). Last van stemmen. Een gecontroleerde (kosten)effectiviteitsstudie naar een op Hallucinaties gerichte Integratieve Therapie (HIT) bij patiënten met schizofrenie of verwante psychose. RGOc-reeks, nummer 3, ISBN-10 90-367-1555-5

Willige van de G., D Wiersma, J. A. Jenner (2003).
Blijvende stemmen de baas. Multi Family Treatment (MFT), een geïntegreerde vorm van nabehandeling voor patiënten met persisterende auditieve hallucinaties en sociale beperkingen. RGOc-reeks, nummer 4, ISBN-10 90-367-1784-1

Wiersma D. (2004). Evidentie voor de Geestelijke Gezondheidszorg, de klinische epidemiologie van psychiatrische stoornissen. Oratie RGOc-reeks, nummer 5, ISBN-10 90-367-1967-4.

Lammeren van A.M.D.N., C.E.J. Ketelaars, E.H. Horwitz, D. Wiersma (2004)
ADHD en ASS bij volwassenen. Onderzoek naar diagnostiek van ADHD en ASS bij normaal begaafde volwassenen, alsmede naar de functionele beperkingen en zorgbehoeften. RGOc-reeks, ISBN-10 90-367-2112-1

Busschbach van J.T., E. Visser, S. Sytema, P. Bastiaansen (2004). Zorg voor mensen met langdurige psychiatrische problematiek. Onderzoek in een regio met een geïntegreerd GGz-aanbod. RGOc-reeks, nummer 7, ISBN-10 90-367-1968-2

Boer den P.C.A.M., D. Wiersma, I.A.M. ten Vaarwerk, A.D. Stant, R.J. van den Bosch (2005). Cognitieve Zelftherapie voor patiënten met chronisch-recidiverende depressie of (gegeneraliseerde) angststoornis. RGOc -reeks, nummer 8, ISBN-10 90-367-2303-5

Busschbach van J.T., E. Visser, S. Sytema, D. Wiersma (2006). Blijvend aan het werk. Onderzoek naar het lange termijnresultaat van arbeidsrehabilitatie bij DAAT-Drenthe. RGOc-reeks, nummer 9, ISBN-10 90-367-2565-8

Castelein S., R. Bruggeman, J.T. van Busschbach, D. Wiersma (2006). Begeleide

lotgenotengroepen voor mensen met een psychose. Een gecontroleerde effectiviteitsstudie. RGOc-reeks, nummer 10, ISBN-13 978-90-367-2431-9

Castelein S., P.J. Mulder, R. Bruggeman (2006). Draaiboek voor het begeleiden van een lotgenotengroep voor mensen met een psychose. RGOc-reeks, nummer 11, ISBN-10 90-367-2683-2. [alleen verkrijgbaar via Kenniscentrum Schizofrenie in combinatie met training]

Boer den P.C.A.M. (2006). Cognitive self-therapy. A contribution to long-term treatment of depression and anxiety. Proefschrift. RGOc-reeks, nummer 12, ISBN-10 90-367-2714-6

Wunderink L. (2006). Antipsychotic Treatment Strategies and Early Course of First Episode Psychosis. Proefschrift. RGOc-reeks, nummer 13, ISBN-10 90-367-2812-6
Wolters K.J.K. J.T. van Busschbach, E.G. Soldaat, J.C.A. de Bruijn (2006). De GGz aan huis bij de huisarts. Een beschrijvend onderzoek naar de inzet van sociaal psychiatrisch verpleegkundigen in huisartspraktijken rondom Emmen en Stadskanaal. RGOc-reeks, nummer 14, ISBN-10 90-367-1966-6

Stant D. (2007). Economic evaluation in mental healthcare. Assessing the cost-effectiveness of interventions for patients with major depressive disorder or schizophrenia in the context of the Dutch healthcare system. Proefschrift. RGOc-reeks, nummer 15, ISBN 978-90-36729-59-8.

Heer-Wunderink de C., A.D. Caro-Nienhuis, S. Sytema, D. Wiersma (2007). UTOPIA. Uit en Thuis: Onderzoek naar de Participerende Instellingen van de RIBW Alliantie. RGOc-reeks, nummer 16, ISBN 978-90-367-3106-5.

Giel R. (2007). Onderweg. Even blijven staan, kijken en dan zien
Gedichten en observaties van Rob Giel gedurende zijn dienstreizen, met name voor de WHO. Bijzondere uitgave in de RGOc-reeks, ISBN 978-90-367-3210-9
[Alleen verkrijgbaar via de boekhandel]

Groot de M (2008). Bereaved by Suicide. Family-based cognitive-behavior therapy to prevent adverse health consequences among first-degree relatives and spouses. Proefschrift. RGOc-reeks, nummer 17, ISBN 978-90-367-3368-7

Castelein S. (2009). Guided peer support groups for psychosis. A randomized controlled trial. Proefschrift. RGOc-reeks, nummer 18, ISBN 978-90-367-3689-3

Caro-Nienhuis A.D. (RGOc), C. de Heer-Wunderink (RGOc), A. Dompeling (GGz Cliëntenplatform), A. Messchendorp (GGz Cliëntenplatform), L. Tan (GGz Cliëntenplatform) (2009). Nait soez'n, moar deurbroez'n met elkaar: de psychiatrische woonzorg is nog lang niet klaar. Een onderzoek naar de woonkwaliteit van zelfstandig

wonenden met langdurige psychiatrische problematiek in Groningen. RGOc-reeks, nummer 19, ISBN 978-90-367-3848-4

Busschbach van J. T., Kerstin J.K. Wolters, Hannie P.A.T. Boumans (2009). Betrokkenheid in kaart gebracht. Ontwikkeling en gebruik van de Triadekaart in de GGZ. RGOc-reeks nummer 20, ISBN 978-90-367-3890-3

Al Hadithy A.F.Y. (2009). Pharmacogenetics of Antipsychotic-Induced Parkinsonism and Tardive Dyskinesia: a Focus on African-Caribbeans and Slavonic Caucasians. Proefschrift. RGOc-reeks nummer 21, ISBN 978-94-607-0001-9

Heer-Wunderink de C., E. Visser, A.D. Caro-Nienhuis, S. Sytema, D. Wiersma (2009). De RIBW doet mee. Functioneren en tevredenheid van cliënten die woonbegeleiding ontvangen van de RIBW's, de tweede fase van het UTOPIA-onderzoek. RGOc-reeks nummer 22, ISBN 978-90-367-4094-4

Schorr S.G. (2010). Drug safety in patients with psychotic disorders. Proefschrift RGOc-reeks nummer 23, ISBN 978-94-607-0007-1

Wolters H.A. (2010). Desired and undesired effects of antipsychotic treatment from a patients perspective: the psychometric evaluation of a self-rating instrument. Proefschrift. RGOc-reeks nummer 24, ISBN 978-90-367-4129-3

Caro-Nienhuis A.D., C. de Heer-Wunderink, S. Sytema, D. Wiersma (2010). Ontwikkelingen in de RIBW. Tweede prevalentiemeting in het kader van het UTOPIA-onderzoek. RGOc-reeks nummer 25, ISBN 978-90-367-4431-7

Bartels A. (2011). Auditory hallucinations in childhood. Proefschrift, RGOc-reeks nummer 26, ISBN 978-94-6070-036-1
Vehof J. (2011). Personalized pharmacotherapy of psychosis. Clinical and pharmacogenetic approaches. Proefschrift, RGOc-reeks nummer 27, ISBN 978-90-367-4931-2
Aerts L. (2011). Vaktherapieën. RGOc-reeks nummer 28.

Boonstra N. (2011). Early detection of psychosis; why should we care? RGOc-reeks nummer 29.

Curriculum Vitae

Nynke Boonstra werd op 3 december 1975 geboren in Leeuwarden. Ze behaalde in 1993 haar HAVO diploma aan het Slauerhoff College in Leeuwarden. Hierna studeerde ze Verpleegkunde aan de Noordelijk Hogeschool Leeuwarden en behaalde in 1997 haar diploma. Vervolgens studeerde ze verplegingswetenschap aan de faculteit gezondheidswetenschappen aan de Universiteit van Maastricht locatie Groningen. Van 1997 tot 2001 was ze werkzaam als verpleegkundige bij GGZ Friesland eerst in Franeker en vanaf 1998 in Heerenveen op een klinische opname afdeling voor chronisch psychiatrische patiënten. Sinds 2001 is ze in deeltijd werkzaam voor de afdeling wetenschappelijk onderzoek en opleiding van GGZ Friesland, eerst als onderzoeksassistente en sinds 2003 als onderzoeker. Sinds 2008 is ze betrokken bij de implementatie van het VIP team waar ze tot op heden ondersteuning biedt bij onderzoek en evidence based werken. Onderdeel van het VIP team is het early detection team dat zich richt op de detectie van jongeren met een verhoogd risico op het ontwikkelen van een eerste psychose. Dit team is opgestart vanuit de EDIE.NL studie. Nynke werkte als onderzoekscoördinator voor Friesland aan deze studie. Nynke is als deelnemersraadslid van het kenniscentrum Phrenos medeorganisator van het jaarlijkse schizofreniecongres in Zwolle. Namens V&VN heeft ze een bijdrage geleverd aan het hoofdstuk zorg in de multidisciplinaire richtlijn schizofrenie 2011. Ook is Nynke sinds 2010 actief betrokken de de opzet en implementatie van het zorgprogramma Psychosen en Rehabilitatie binnen GGZ Friesland, als directielid en programma specialist.

Daarnaast werkt ze sinds 2001 als hogeschool docent aan de NHL hogeschool op de afdeling zorg waar ze les geeft over psychiatrie, evidence based werken en onderzoeksmethodologie aan verpleegkundigen in opleiding. Ook is ze projectleider bij het kenniscentrum zorg en welzijn van de NHL hogeschool voor de opleiding POH-GGZ. Sinds 1 april 2011 is Nynke opleider van de GGZ-VS voor GGZ Friesland en VNN.

Nynke woont samen met Marcel en samen hebben ze een zoon, Daniël van 3 jaar.