Early detection of psychosis; why should we care?
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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 a 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).
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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
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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 diagnostic 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
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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.
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