The social and symptomatic course of eearly-onset schizophrenia. Five year follow-up of a psychosocial intervention

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CHAPTER 1

GENERAL INTRODUCTION

Psychotic disorders have been described since ancient times. Abnormal behaviours and psychiatric conditions under different names, are found in the literature and early scientific writings (Van der Ploeg, 1997).

Kraepelin (1899) described several psychiatric conditions under one diagnostic classification, namely 'dementia praecox'. Initially, Kraepelin sought the origin of this disorder in hereditary factors, later also in 'autotoxines' of the brain (Kraepelin, 1919). According to this author, dementia praecox was characterised by progressive blunting with a characteristic age of onset (praecox), resulting in weakness of the mind (dementia). Characteristic of this state were delusions, flat affect and indifference, lack of psychological independence, a-motivation, negativism, impulsive actions, stereotypy and mannerism. Although remissions were thought possible, Kraepelin assumed that symptoms could return under the slightest provocation.

E. Bleuler (1911), who introduced the term 'schizophrenia', also sought the aetiology of the illness in biological factors. Characteristic of the illness, according to Bleuler, was a split between mental functions. He specified a hierarchy of primary symptoms (associative and affective disturbances, and ambivalence) and secondary symptoms (e.g. hallucinations and delusions). While focusing on symptoms rather than on course, Bleuler observed that schizophrenia does not always result in mental deterioration.

The observation of heterogeneity in outcome led M. Bleuler (1978) to describe the course of schizophrenia according to two types of illness onset (acute and chronic), two types of course (simple and undulating), and two types of end state ('recovered or mild impairment' and 'moderate or severe impairment'). Ciompi (1980) conducted a long-term study (37

years from first hospitalisation on average) on the course of schizophrenia. He distinguished eight course types, consisting of combinations of Bleuler's patterns. From the 228 patients with a diagnosis of schizophrenia, 50% turned out to have had an undulating course, whereas 20% were considered as recovered, and 43% as improved. The most frequent course combinations were: an undulating course with an acute onset, followed by an end state, characterised as 'recovery or mild' (25%), and a simple course with a chronic onset and a 'moderate or severe' end state (24%).

Although Harding (1988) showed considerable differences in frequencies of the eight course types between three studies (Bleuler, 1978; Ciompi, 1980; Harding et al., 1987), these studies clearly demonstrated the heterogeneous course of schizophrenia, contradicting the pessimistic view regarding schizophrenia, originating from the Kraepelinian standpoint, as it is still held by many people (McGorry, 1999).

The heterogeneity in outcome regarding schizophrenia is also reflected in the level of social functioning. Bleuler (1978) concluded that 43% of his sample of 208 patients with a diagnosis of schizophrenia, had little or no impairment in social functioning. Ciompi (1980) defined social adaptation in terms of having social relationships without conflict, poor social relationships and being dependent, and judged one-third of his sample to have a good or satisfactory social adaptation. Harding et al. (1987) used items of the Strauss & Carpenter (1977) prognostic scale and found two-thirds to four-fifths of the subjects to be improved socially. These early studies on social functioning, although methodologically heterogeneous, indicate that social limitations in patients with psychotic disorders are considerable.

A MODEL OF VULNERABILITY AND STRESS REGARDING SCHIZOPHRENIA

The heterogeneous outcome in schizophrenia implies that the search for predictors of the course of the illness has become an important goal, especially during the early phase of the illness (Carpenter & Strauss, 1991). The selection from different treatment strategies in the early phase of the illness becomes possible when robust predictors can be identified. Predictors may also contribute to theory development regarding the pathogenesis of the illness. Regarding the aetiology and course of schizophrenia several models were proposed,

which were reviewed by Zubin (1972). Zubin & Spring (1977) classified these models in three categories: environmental, social-psychological and internal-biological, and sought for common characteristics among models that seek the determinants of schizophrenia in biological factors and those that regard the illness as a psychosocial disorder.

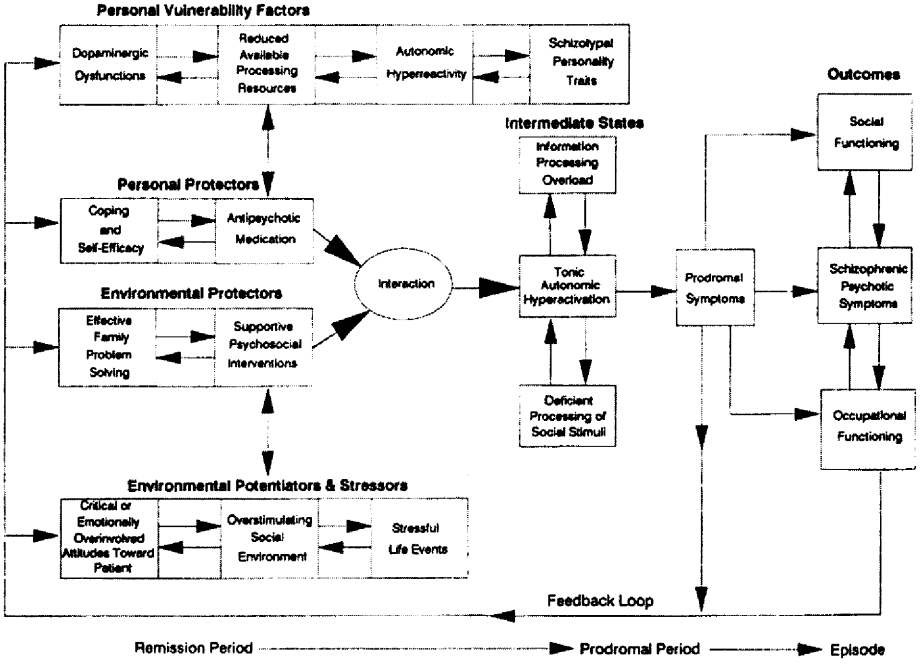
In the vulnerability model of Zubin & Spring (1977) it is assumed that every person has a vulnerability in some degree, which can express itself in a psychotic episode when the personal tolerance threshold is exceeded by the impact of stressors. According to these authors, stressors can be endogenous, such as biochemical or neurophysiological changes, caused for instance by malnutrition, toxic ingestion or infections; or exogenous: the life events, such as marriage, divorce or promotion. Two components are distinguished in vulnerability: 1) inborn vulnerability as it is included in the genes; and 2) vulnerability that can be acquired by traumas or diseases, but also by experiences with other people. In this model schizophrenia is seen as an episodic illness, like depression, epilepsy, or allergy, whereas vulnerability is seen as the primary persistent characteristic, which may or may not give rise to a psychotic episode (Zubin et al., 1983).

The vulnerability and stress factors were depicted in a model (Figure 1.1) by Nuechterlein et al. (1992a). In the premorbid and in the remission period, personal vulnerability factors and personal protectors influence each other, as well as environmental protectors, and environmental potentiators and stressors. Fluctuations of, and the interplay between the four factors may result in an intermediate state, preceding the onset or return of psychotic symptoms. In the intermediate state, the overloaded information processing, tonic autonomic hyperactivation and deficient processing of social stimuli interact with each other and may result in a prodromal episode. A feedback loop displays the possibility that prodromal symptoms can affect the personal and environmental vulnerability and stress factors, which in turn affect the intermediate state and the prodromal symptoms. When a threshold of prodromal symptoms is exceeded, a psychotic episode results, which affects social and occupational functioning.

The vulnerability-stress model is considered heuristic because it provides a framework of global entities which can be adjusted or extended when new research findings become available. For instance, not all factors of the personal vulnerability are known, which is true in particular for the biological markers (Goldstein, 1987). Also, the threshold of vulnerability is a hypothetical construct, which is difficult to establish for a particular

person. The model is tentative because the associations between the variables and the directions of the relationships are hypothesised, which means that not all relationships and interactions have empirically been confirmed. Nevertheless, the model offers a framework in which much of the results from different research traditions can be organised and interpreted. It also offers the possibility to actually determine the associations as found in the literature concerning the course of schizophrenia in an integrative way. Nuechterlein et al. (1992b) for instance, tested the effects of family factors, patients illness characteristics and living conditions, and their interrelationships regarding the occurrence of psychotic relapse.

Figure 1.1 A tentative heuristic framework for some of the possible psychobiological vulnerability factors, nonspecific environmental stressors, and protective factors in schizophrenic relapse and illness course



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The vulnerability-stress model is also the framework of the present follow-up study, as it was for the preceding intervention study (Linszen, 1993). The focus of the present study is the 5-year course of early-onset schizophrenia and its predictors: the risk and protective factors. However, not all factors of vulnerability and stress are included. Biological factors for instance are missing in the present study, as well as stressful life events, because they were not the focus of the intervention study. Central in the present study are the intervention in the early phase of the illness as a possible protector, and parental expressed emotion as a an environmental stressor. These two factors are described below.

EXPRESSED EMOTION

In Figure 1.1 it is shown that negative family attitudes can be an environmental source of stress, which can trigger a psychotic episode. Critical and emotionally overinvolved, as well as hostile attitudes of family members toward a patient, vulnerable for a psychotic episode, are referred to as expressed emotion (EE). Numerous studies have demonstrated the predictive value of EE regarding psychotic relapse. Although a number of studies failed to replicate this effect (Kavanagh, 1992), meta analyses demonstrated EE to be a robust predictor of relapse in schizophrenia (Parker & Hadzi-Pavlovic, 1990; Bebbington & Kuipers, 1994; Butzlaff & Hooley, 1998).

The replicated finding of high EE predicting psychotic relapse, and the efficacy of family interventions in lowering high EE in conjunction with reduced relapse rates, fed the hypothesis that high EE causes psychotic relapse (Brown et al., 1972; Leff et al., 1982).

The causal role of EE regarding relapse was challenged by others. Firstly, it was stated that causality cannot be proven in naturalistic studies. When subjects are not randomly allocated to treatment conditions, the possibility remains that certain characteristics and/or behaviours in the patient elicit negative responses in relatives (Hogarty et al., 1986; Koenigsberg & Handley, 1986; Miklowitz, 1994; Van Os et al., 2001). However, even in randomised trials in which both EE and relapse are measured at the end of the intervention, the direction of the link between EE and relapse cannot be ascertained. Secondly, other variables were mentioned to account for the efficacy of family intervention: reduction of face-to-face contact between patients and high EE relatives, and better medication

compliance in patients receiving family treatment (Falloon et al., 1982; Leff et al., 1982, 1985). A better contact between clinical staff and therapists was also mentioned as a possible confounding factor (Tarrier et al., 1988; Lam, 1991). Thirdly, it was stated that, in order to be a cause of relapse, the level of EE must be a constant characteristic in relatives (Falloon, 1988). McCreadie et al. (1993) pointed out that if the level of EE is not constant, thus not a fixed set of attitudes or traits in relatives, it might be a temporary state, waxing and waning with the patient's mental state. Koenigsberg & Handley (1986), Kuipers & Bebbington (1988) and Lam (1991) pointed out that EE is usually measured at admission, when stress in families is high. A number of studies indeed demonstrated that many relatives changed spontaneously from high to low EE over time (Brown et al., 1972; Dulz & Hand, 1986; Hogarty et al., 1986; Tarrier et al., 1988). However, other studies found evidence for EE as a stable characteristic in relatives (McCreadie et al., 1991, 1993; Huguelet et al., 1995; Nugter et al., 1997; King, 2000).

The method to assess EE has been criticised as well. Firstly, the standard instrument to elicit EE, the Camberwell Family Interview (Vaughn & Leff, 1976), is time consuming. It generally takes 1.5 to 2 hours to administer and 3 to 4 hours to rate. This may impede carrying out repeated measurements of EE, and studies with large samples. Indeed, studies on the course of EE are scarce, and samples are usually small (Mari & Streiner, 1994). Secondly, it was stated that the dichotomous nature of the EE index (low/high) does not reflect the complex nature of family relationships (Kuipers, 1992; Gottschalk & Keatinge, 1993). Moreover, the highest EE score of two relatives is taken as the family profile score. In this way the complementary effect of low EE parents in mixed EE families is not taken into account. Finally, a dichotomous index is less sensitive to change, since smaller changes than from high to low EE cannot be detected.

TREATMENT OF PSYCHOTIC DISORDERS

Antipsychotic medication and psychosocial interventions are considered as personal and environmental protectors in the vulnerability-stress model (Figure 1.1).

Since antipsychotics became available in the 1950s, the treatment of schizophrenia has improved considerably. Long-term studies of first admitted patients show a shift in

favourable outcomes or recoveries from 23% (Bleuler, 1978) through 38% (Wing, 1966) during the pre-neuroleptic era, to 49% (Hegarty et al., 1994) during the neuroleptic era. However, as Birchwood (1999) pointed out, this shift is not solely attributable to neuroleptics. Continuity in care, support and community based treatment may have contributed to this shift. On the other hand, it is not clear whether patients are always compliant to prescribed antipsychotic medication. It is estimated that 40% of patients with schizophrenia discontinue their medication (Young et al., 1986). Discontinuation of antipsychotics appeared to result in a five times higher risk of psychotic relapse in first episode schizophrenia during five years after recovery from a psychosis (Robinson et al., 1999).

Reasons for discontinuation of antipsychotic medication by patients are sought in side effects of the medication, in negative symptoms related to antipsychotics, and also in lack of insight in the illness by the patient, and in social factors like lack of support by family members (Young et al., 1986). Therefore, in order to enhance therapy compliance, psychosocial interventions were developed, not only aimed at providing information about the illness and medication, but also at rehabilitation to enhance social integration. Types of psychosocial intervention are (see for reviews Mueser & Bond, 2000 and Bustillo et al., 2001): case management, vocational rehabilitation, social skills training and cognitive therapy. In some interventions relatives are included, to be informed about the illness, to encourage them to act as co-therapists, to help them to cope better with the patient's illness, and/or to lower the level of expressed emotion (see above). In general, psychosocial interventions are superimposed on treatment with antipsychotic medication, to determine the additional effect of these interventions.

AIM AND GENERAL DESIGN OF THE STUDY

The present study regards the 5-year follow-up of an intervention study that was carried out in the Adolescent Clinic of the Academic Medical Center, Department of Psychiatry in Amsterdam. The main goal of that study was the treatment of patients with schizophrenia in the early phase of the illness. It has been reported that a first episode of schizophrenic symptoms generally takes place between 15 and 30 years of age (Jablensky et al., 1992),

with a later onset for females than for males (Angermeyer & Kühn, 1988). It was hypothesised that intervention in the early phase of the illness could prevent a deteriorating course (Linszen, 1993).

The 15-month intervention programme turned out to have a beneficial effect on the occurrence of psychotic relapses, irrespective of the type of intervention (standard intervention and standard plus family intervention; Linszen et al., 1996). The use of cannabis and high parental expressed emotion were the best predictors of an unfavourable course of the illness (Linszen et al., 1994, 1997). However, 16% to 27% (depending on the type of operationalisation) of the patients relapsed during the 12-month out-patient phase of the intervention programme. This is considerably lower than percentages found in other intervention studies (cf. 20% to 53% of relapsed patients within nine months; Mari & Streiner, 1994). Continuity in care with the same personnel responsible for the patients, and support and education for families, in combination with medication compliance in patients, were probably conducive to this favourable result.

The question was raised whether this effect continued after discharge from the intervention programme. In the present study the course of the illness over five years after discharge from the intervention programme is studied, as well as the level of social functioning (work, study, living arrangements, help from the family etc.).

In the following section the initial intervention study is described briefly (see also Linszen, 1993), followed by the general design of the follow-up study and the specific research questions which form the basis of this thesis.

The Intervention study

The subjects of the study were 97 young individuals (mean age at admission 20.5 years) with, mainly (55%), a first psychotic episode, who were admitted in the Adolescent Clinic between 1986 and 1990.

The intervention programme consisted of an in-patient phase of three months, and an out-patient phase of twelve months. The out-patient phase consisted of a day hospital programme of three months, followed by nine months of community care.

The in-patient phase was aimed at remission or stabilisation of psychotic symptoms, the establishment of an optimal medication dose, and at education about the type and treatment

of the illness. Efforts were made to create an optimal working alliance with parents. Parents were also educated about the illness and medication, and were instructed to create low stress levels for their child.

During the out-patient phase, individual contacts occurred biweekly during the first five months, and monthly thereafter. Patients were further taught about the illness, prodromal symptoms and the risks of psychotic relapse. They also received medication management training, learned problem-solving techniques, and received help with the organisation of employment, education and financial support.

During the out-patient phase, half of the patients and their families received an additional family treatment, based on the behavioural family management of Falloon et al. (1984). Supporting parents and psycho-education, training in communication and problem-solving skills with families, were the main ingredients of the family intervention. The frequency of the family sessions was equal to that of the standard treatment.

Patients and parents were randomly allocated to one of the two intervention conditions (standard intervention and standard plus family intervention) after being stratified into low and high parental expressed emotion (EE; see above). Parental EE was assessed with the Camberwell Family Interview (Vaughn & Leff, 1976), which interview was held within eleven days on average after admission.

During intervention parental EE was assessed two times with a shorter method than the Camberwell Family Interview: the Five Minute Speech Sample (Magaña et al., 1986). These assessments were carried out at the beginning of the out-patient phase of the intervention, the point in time at which families were randomised over the two intervention conditions, and after the completion of the out-patient phase.

The follow-up study

The follow-up study was carried out in two waves. The first wave took place in 1992 (Follow-Up I). At that point in time the follow-up period varied from 17 to 55 months (mean 34 months). This was caused by the fact that the patients had finished the intervention programme between 1987 and 1991. For this reason a second wave was planned (Follow-Up II) to establish the course of the illness and social functioning over five years. This wave was carried out in 1997/1998 (mean 8 years, range 6-10 years after discharge). At both

follow-up waves the Five Minute Speech Sample was elicited again with parents, thus making a longitudinal analysis of the level of expressed emotion possible.

The first research question regards the operationalisation of the expressed emotion (EE) concept. As noted above, the level of EE is conventionally expressed as low and high expressed emotion. This dichotomous index does not reflect the complex nature of family interactions. For instance one critical remark more or less can characterise the family as high EE (Hatfield et al., 1987). Moreover, longitudinal analysis with repeated measures on dichotomous variables like EE is difficult, if not impossible, and small changes in the level of EE are hard to detect with such a measure. Therefore, in ***Chapter 2*** a composite scale is constructed, using the nine items of the Five Minute Speech Sample (FMSS). In ***Chapter 3*** the association of psychotic relapse as assessed during Follow-up I with the EE scales as found in Chapter 2, as well as with the original dichotomous FMSS-EE index is investigated.

The second research question concerns the course of parental EE and its association with the course of the illness. An important issue regarding EE is, whether it is a steady state in relatives, or a fluctuating response to stressful situations. Long-term research on EE is uncommon. Most studies regarding the stability of EE were carried out over 9, 12 or 18 months. In these studies percentages of high EE families were compared over different points in time. A number of studies found EE decreasing over time (see Stirling et al., 1993 and Mari & Streiner, 1994 for reviews; and Scazufca & Kuipers, 1998). Other studies found EE to remain stable, either in parents who were not involved in family intervention (McCreadie et al., 1993; Huguelet et al., 1995; King, 2000) or irrespective of family intervention (McCreadie et al., 1991; Nugter et al., 1997).

In ***Chapter 4*** the course of parental EE is analysed over nine years on average. The FMSS was assessed two times during the 12-month out-patient phase of the intervention programme and two times during follow-up (i.e. at 34 months and at 8 years on average after discharge). Again, the scale structure as found in Chapter 2 is used, as well as the dichotomous FMSS-EE index. In addition the course of parental EE is compared across the two intervention conditions (standard intervention and standard plus family intervention). Furthermore, the association between psychotic episodes during five years of follow-up and

EE at four points in time is investigated. With the present design it is possible to get more clues about the role of EE regarding psychotic relapse: is it a predictor, and possibly a cause, of psychotic relapse in patients (EE as assessed two times during intervention); is it merely associated, and possibly a consequence, of psychotic relapse (the third assessment of EE, falling within the 5-year follow-up period); or is psychotic relapse a predictor of EE (the fourth assessment of EE, which took place after the 5-year period)?

A third question regards the course of the illness in relation to social functioning. Bleuler (1974) observed that the development of the subsequent course takes place in the first five years of the illness. Carpenter & Strauss (1991) studied outcome in schizophrenia after 2, 5 and 11 years. They found significant impairments at each point in time, but no evidence for a progressive deteriorating course. Investigating the course of the illness in young patients with early-onset schizophrenia may reveal this plateau effect (McGlashan, 1988; Birchwood, 1999).

Research on the course of schizophrenia was focused for many years on the onset and course of psychiatric symptoms (Strauss, 1975; Engelhardt & Rosen, 1976). Since treatment of patients with psychiatric symptoms shifted from long-term periods in mental hospital to out-patient services, after a short period in hospital, the research of social functioning has become increasingly important, because schizophrenia implies severe social impairments. For this reason social functioning has become an important outcome measure in schizophrenia.

A number of instruments were developed to assess social functioning (Platt et al., 1980; WHO, 1985; Birchwood et al., 1990; Wiersma et al., 1993). In other studies several indicators for social functioning were used: living within the community, employment, having a relationship, social contacts, and social abilities (Strauss & Carpenter, 1974, 1977; Falloon et al., 1982; Leff et al., 1989; Xiong et al., 1994; McFarlane et al., 1995; Wieselgren & Lindström, 1996; Häfner et al., 1998; Liberman et al., 1998).

Chapter 5 describes the course of schizophrenia, expressed as months with psychotic symptoms, and social functioning, expressed as months in institutions for psychiatric patients, months of structural activities and help from the family.

The fourth research question regards the prediction of the course of the illness. It is assumed that the development of the illness takes place in the first five years of the illness, the critical period (Birchwood & Macmillan, 1993). When robust predictors are available, it is possible to offer patients differentiated psychosocial interventions, according to their expected needs.

The vulnerability-stress model as described above, provides the possibility to extend the protectors and stressors, as well as the vulnerability factors. Linszen et al. (1997) reviewed predictor studies regarding psychotic relapse. The predictors as found in the research literature were: gender, education, the Strauss & Carpenter prognostic scale (Kokes et al., 1977), the premorbid adjustment scale of Goldstein (Kokes et al., 1977), parental expressed emotion (Vaughn & Leff, 1976), socio-economic status, one parent household, age at first psychotic episode, type of illness onset (acute, subacute, chronic), prior psychotic episodes, diagnosis (schizophrenia v. schizophrenia related disorders), psychopathology at the end of the in-patient phase of the intervention (Breier et al., 1991), the use of cannabis (Linszen et al., 1994), and duration of untreated illness.

In ***Chapter 6*** the fourteen variables as described by Linszen et al. (1997) are investigated as possible predictors of the 5-year course of the illness, and aspects of social functioning, i.e. living in institutions for psychiatric patients, structural activities and help from the family. To the fourteen possible predictors, four more variables were added, because they appeared to be predictive in recent research literature, and because they were also assessed in the Linszen et al. intervention study: prior admissions (Lay et al., 2000), ethnic group (McKenzie et al., 2001), living with parents before admission (Nuechterlein et al., 1992b), and compliance with antipsychotic medication (Robinson et al., 1999) during intervention. Intervention condition is included as a possible predictor as well, because an effect of this variable was found on living in institutions for psychiatric patients (Chapter 5).

The outcome variables and the (possible) predictors are included in one model, using path analysis. In this way it is possible to determine the relative effect of the predictor variables, not only on psychotic relapse, but also on the other outcome variables, and the interrelationships between outcome variables. Moreover, path analysis provides the possibility to fill in the vulnerability-stress model, partially, since we have no biological variables for the present sample.

REFERENCES

Angermeyer, M.C. & Kühn, L. (1988) Gender differences in age at onset of schizophrenia. An overview. *European Archives of Psychiatry and Neurological Sciences*, 237, 351-364.

Bebbington, P. & Kuipers, L. (1994) The predictive utility of expressed emotion in schizophrenia: an aggregate analysis. *Psychological Medicine*, 24, 707-718.

Birchwood, M. (1999) Early intervention in psychosis: the critical period. In: McGorry, P.D. & Jackson, H.J. (Eds.) *The Recognition and Management of Early Psychosis. A Preventive Approach*. Cambridge, UK: Cambridge University Press.

Birchwood, M. & Macmillan, F. (1993) Early intervention in schizophrenia. *Australian and New Zealand Journal of Psychiatry*, 27, 374-378.

Birchwood, M., Smith, J., Cochrane, R., Wetton, S. & Copestake, S. (1990) The social functioning scale. The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. *British Journal of Psychiatry*, 157, 853-859.

Bleuler, E. (1911) *Dementia Praecox oder die Gruppe der Schizophrenien*. [Dementia Praecox or the Group of Schizophrenias]. Leipzig, Germany: Franz Deuticke.

Bleuler, M. (1974) The long-term course of schizophrenic psychoses. *Psychological Medicine*, 4, 244-254.

Bleuler, M. (1978) *The Schizophrenic Disorders. Long-Term Patient and Family Studies*. (translated by S.M. Clemens). New Haven: Yale University Press.

Breier, A., Schreiber, J.L., Dyer, J. & Pickar, D. (1991) National Institute of Mental Health longitudinal study of chronic schizophrenia. Prognosis and predictors of outcome. *Archives of General Psychiatry*, 48, 239-246.

Brown, G.W., Birley, J.L.T. & Wing, J.K. (1972) Influence of family life on the course of schizophrenic disorders: a replication. *British Journal of Psychiatry*, 121, 241-258.

Bustillo, J.R., Lauriello, J., Horan, W.P. & Keith, S.J. (2001) The psychosocial treatment of schizophrenia: an update. *American Journal of Psychiatry*, 158, 163-175.

Butzlaff, R.L. & Hooley, J.M. (1998) Expressed emotion and psychiatric relapse. A meta-analysis. *Archives of General Psychiatry*, 55, 547-552.

Carpenter, W.T. Jr. & Strauss, J.S. (1991) The prediction of outcome in schizophrenia. IV. Eleven-year follow-up of the Washington IPSS cohort. *Journal of Nervous and Mental Disease*, 179, 517-525.

Ciompi, L. (1980) Catamnestic long-term study on the course of life and aging of schizophrenics. *Schizophrenia Bulletin*, 6, 606-618.

Dulz, B. & Hand, I. (1986) Short-term relapse in young schizophrenics: can it be predicted and affected by family (CFI), patient, and treatment variables? An experimental study. In: Goldstein, M.J., Hand, I. & Hahlweg, K. (Eds.) *Treatment of Schizophrenia. Family Assessment and Intervention*. Berlin, Germany: Springer-Verlag.

Engelhardt, D.M. & Rosen, B. (1976) Implications of drug treatment for the social rehabilitation of schizophrenic patients. *Schizophrenia Bulletin*, 2, 454-462.

Falloon, I.R.H. (1988) Expressed emotion: current status. *Psychological Medicine*, 18, 269-274.

Falloon, I.R.H., Boyd, J.L. & McGill, C.W. (1984) *Family Care of Schizophrenia. A Problem-Solving Approach to the Treatment of Mental Illness*. New York, NY: The Guilford Press.

Falloon, I.R.H., Boyd, J.L., McGill, C.W., Razani, J., Moss, H.B. & Gilderman, A.M. (1982) Family management in the prevention of exacerbations of schizophrenia. *New England Journal of Medicine*, 306, 1437-1440.

Goldstein, M.J. (1987) Psychosocial issues. *Schizophrenia Bulletin*, 13, 157-171.

Gottschalk, L.A. & Keatinge, C. (1993) Influence of patient caregivers on course of patient illness: "expressed emotion" and alternative measures. *Journal of Clinical Psychology*, 49, 898-912.

Häfner, H., Hambrecht, M., Löffler, W., Munk-Jørgensen, P. & Riecher-Rössler, A. (1998) Is schizophrenia a disorder of all ages? A comparison of first-episode and early course across the life-cycle. *Psychological Medicine*, 28, 351-365.

Harding, C.M. (1988) Course types in schizophrenia: an analysis of European and American studies. *Schizophrenia Bulletin*, 14, 633-643.

Harding, C.M., Brooks, G.W., Ashikaga, T., Strauss, J.S. & Breier, A. (1987) The Vermont longitudinal study of persons with severe mental illness. II. Long-term outcome of subjects who retrospectively met DSM-III criteria for schizophrenia. *American Journal of Psychiatry*, 144, 727-735.

Hatfield, A.B., Spaniol, L. & Zipple, A.M. (1987) Expressed emotion: a family perspective. *Schizophrenia Bulletin*, 13, 221-226.

Hegarty, J.D., Baldessarini, R.J., Tohen, M., Waternaux, C. & Oepen, G. (1994) One hundred years of schizophrenia: a meta-analysis of the outcome literature. *American Journal of Psychiatry*, 151, 1409-1416.

Hogarty, G.E., Anderson, C.M., Reiss, D.J., Kornblith, S.J., Greenwald, D.P., Javna, C.D. & Madonia, M.J. (1986) Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia. I. One-year effects of a controlled study on relapse and expressed emotion. *Archives of General Psychiatry*, 43, 633-642.

Huguelet, Ph., Favre, S., Binyet, S., Gonzalez, Ch. & Zabala, I. (1995) Stabilité et rôle pronostique de l'émotion exprimée des familles dans l'évolution d'une cohorte de patients schizophrènes suivis durant cinq ans. [Stability and predictive role of emotions, expressed by families in the development of a cohort of schizophrenic patients in the course of 5 years]. *Annales Médico-Psychologiques*, 153, 687-695.

Jablensky, A., Sartorius, N., Ernberg, G., Anker, M., Korten, A., Cooper, J.E., Day, R. & Bertelsen, A. (1992) Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychological Medicine* (Monograph supplement 20). Cambridge, UK: Cambridge University Press.

Kavanagh, D.J. (1992) Recent developments in expressed emotion and schizophrenia. *British Journal of Psychiatry*, 160, 601-620.

King, S. (2000) Is expressed emotion cause or effect in the mothers of schizophrenic young adults? *Schizophrenia Research*, 45, 65-78.

Koenigsberg, H.W. & Handley, R. (1986) Expressed emotion: from predictive index to clinical construct. *American Journal of Psychiatry*, 143, 1361-1373.

Kokes, R.F., Strauss, J.S. & Klorman, R. (1977) Premorbid adjustment in schizophrenia. Part II. Measuring premorbid adjustment: the instruments and their development. *Schizophrenia Bulletin*, 3, 186-213.

Kraepelin, E. (1899) *Psychiatrie. Ein Lehrbuch für Studierende und Aerzte*. [Psychiatry. A Textbook for Students and Physicians]. Leipzig, Germany: Johann Ambrosius Barth.

Kraepelin, E. (1919) *Dementia Praecox and Paraphrenia*. (translated by R.M. Barclay, reprint 1971). Huntington, NY: Krieger Publishing.

Kuipers, L. (1992) Expressed emotion in 1991. *Social Psychiatry and Psychiatric Epidemiology*, 27, 1-3.

Kuipers, L. & Bebbington, P. (1988) Expressed emotion research in schizophrenia: theoretical and clinical implications. *Psychological Medicine*, 18, 893-909.

Lam, D.H. (1991) Psychosocial family intervention in schizophrenia: a review of empirical studies. *Psychological Medicine*, 21, 423-441.

Lay, B., Blanz, B., Hartmann, M. & Schmidt, M.H. (2000) The psychosocial outcome of adolescent-onset schizophrenia: a 12-year followup. *Schizophrenia Bulletin*, 26, 801-816.

Leff, J., Berkowitz, R., Shavit, N., Strachan, A., Glass, I. & Vaughn, C.E. (1989) A trial of family therapy v. a relatives group for schizophrenia. *British Journal of Psychiatry*, 154, 58-66.

Leff, J., Kuipers, L., Berkowitz, R., Eberlein-Vries, R. & Sturgeon, D. (1982) A controlled trial of social intervention in the families of schizophrenic patients. *British Journal of Psychiatry*, 141, 121-134.

Leff, J., Kuipers, L., Berkowitz, R. & Sturgeon, D. (1985) A controlled trial of social intervention in the families of schizophrenic patients: two year follow-up. *British Journal of Psychiatry*, 146, 594-600.

Liberman, R.P., Wallace, C.J., Blackwell, G., Kopelowicz, A., Vaccaro, J.V. & Mintz, J. (1998) Skills training versus psychosocial occupational therapy for persons with persistent schizophrenia. *American Journal of Psychiatry*, 155, 1087-1091.

Linszen, D.H. (1993) *Recent Onset Schizophrenic Disorders: Outcome, Prognosis and Treatment*. Amsterdam, The Netherlands: University of Amsterdam, Department of Psychiatry. Thesis.

Linszen, D.H., Dingemans, P.M. & Lenior, M.E. (1994) Cannabis abuse and the course of recent-onset schizophrenic disorders. *Archives of General Psychiatry*, 51, 273-279.

Linszen, D.H., Dingemans, P.M., Nugter, M.A., Van der Does, A.J.W., Scholte, W.F. & Lenior, M.E. (1997) Patient attributes and expressed emotion as risk factors for psychotic relapse. *Schizophrenia Bulletin*, 23, 119-130.

Linszen, D., Dingemans, P., Van der Does, J.W., Nugter, A., Scholte, P., Lenior, R. & Goldstein, M.J. (1996) Treatment, expressed emotion and relapse in recent onset schizophrenic disorders. *Psychological Medicine*, 26, 333-342.

Magaña, A.B., Goldstein, M.J., Karno, M., Miklowitz, D.J., Jenkins, J. & Falloon, I.R.H. (1986) A brief method for assessing expressed emotion in relatives of psychiatric patients. *Psychiatry Research*, 17, 203-212.

Mari, J.J. & Streiner, D.L. (1994) An overview of family interventions and relapse on schizophrenia: meta-analysis of research findings. *Psychological Medicine*, 24, 565-578.

McCreadie, R.G., Phillips, K., Harvey, J.A., Waldron, G., Stewart, M. & Baird, D. (1991) The Nithsdale schizophrenia surveys. VIII. Do relatives want family intervention - and does it help? *British Journal of Psychiatry*, 158, 110-113.

McCreadie, R.G., Robertson, L.J., Hall, D.J. & Berry, I. (1993) The Nithsdale Schizophrenia Surveys. XI. Relatives' expressed emotion. Stability over five years and its relation to relapse. *British Journal of Psychiatry*, 162, 393-397.

McFarlane, W.R., Lukens, E., Link, B., Dushay, R., Deakins, S.A., Newmark, M., Dunne, E.J., Horen, B. & Toran, J. (1995) Multiple-family groups and psychoeducation in the treatment of schizophrenia. *Archives of General Psychiatry*, 52, 679-687.

McGlashan, T.H. (1988) A selective review of recent North American long-term followup studies of schizophrenia. *Schizophrenia Bulletin*, 14, 515-542.

McGorry, P.D. (1999) 'A stitch in time' ... The scope of preventive strategies in early psychosis. In: McGorry, P.D. & Jackson, H. (Eds.) *The Recognition and Management of Early Psychosis. A Preventive Approach*. Cambridge, UK: Cambridge University Press.

McKenzie, K., Samele, C., Van Horn, E., Tattan, T., Van Os, J. & Murray, R. (2001) Comparison of the outcome and treatment of psychosis in people of Caribbean origin living in the UK and British whites. *British Journal of Psychiatry*, 178, 160-165.

Miklowitz, D.J. (1994) Family risk indicators in schizophrenia. *Schizophrenia Bulletin*, 20, 137-149.

Mueser, K.T. & Bond, G.R. (2000) Psychosocial treatment approaches for schizophrenia. *Current Opinion in Psychiatry*, 13, 27-35.

Nuechterlein, K.H., Dawson, M.E., Gitlin, M., Ventura, J., Goldstein, M.J., Snyder, K.S., Yee, C.M. & Mintz, J. (1992a) Developmental processes in schizophrenic disorders: longitudinal studies of vulnerability and stress. *Schizophrenia Bulletin*, 18, 387-425.

Nuechterlein, K.H., Snyder, K.S. & Mintz, J. (1992b) Paths to relapse: possible transactional processes connecting patient illness onset, expressed emotion, and psychotic relapse. *British Journal of Psychiatry*, 161 (Suppl. 18), 88-96.

Nugter, A., Dingemans, P., Van der Does, J.W., Linszen, D. & Gersons, B. (1997) Family treatment, expressed emotion and relapse in recent onset schizophrenia. *Psychiatry Research*, 72, 23-31.

Parker, G. & Hadzi-Pavlovic, D. (1990) Expressed emotion as a predictor of schizophrenic relapse: an analysis of aggregated data. *Psychological Medicine*, 20, 961-965.

Platt, S., Weyman, A., Hirsch, S.R. & Hewett, S. (1980) The social behaviour assessment schedule (SBAS): rationale, contents, scoring and reliability of a new interview schedule. *Social Psychiatry*, 15, 43-55.

Robinson, D., Woerner, M.G., Alvir, J.M.J., Bilder, R., Goldman, R., Geisler, S., Koreen, A., Sheitman, B., Chakos, M., Mayerhoff, D. & Lieberman, J.A. (1999) Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Archives of General Psychiatry*, 56, 241-247.

Scazufca, M. & Kuipers, E. (1998) Stability of expressed emotion in relatives of those with schizophrenia and its relationship with burden of care and perception of patients' social functioning. *Psychological Medicine*, 28, 453-461.

Stirling, J., Tantam, D., Thomas, P., Newby, D., Montague, L., Ring, N. & Rowe, S. (1993) Expressed emotion and schizophrenia: the ontogeny of EE during an 18-month follow-up. *Psychological Medicine*, 23, 771-778.

Strauss, J.S. (1975) A comprehensive approach to psychiatric diagnosis. *American Journal of Psychiatry*, 132, 1193-1197.

Strauss, J.S. & Carpenter, W.T. Jr. (1974) The prediction of outcome in schizophrenia. II. Relationships between predictor and outcome variables: a report from the WHO International Pilot Study of Schizophrenia. *Archives of General Psychiatry*, 31, 37-42.

Strauss, J.S. & Carpenter, W.T. Jr. (1977) Prediction of outcome in schizophrenia. III. Five-year outcome and its predictors. *Archives of General Psychiatry*, 34, 159-163.

Tarrier, N., Barrowclough, C., Vaughn, C., Bamrah, J.S., Porceddu, K., Watts, S. & Freeman, H. (1988) The community management of schizophrenia. A controlled trial of a behavioural intervention with families to reduce relapse. *British Journal of Psychiatry*, 153, 532-542.

Van der Ploeg, G.J. (1997) Inleiding in de geschiedenis van het schizofrenie-concept. [Introduction to the history of the schizophrenia concept]. In: Van der Ploeg, G.J. & Linszen, D.H. (Eds.) *Van Dementia Praecox tot de Groep van Schizofrenieën. Twee Pogingen tot Begripsbepaling van een Psychiatrisch Ziektebeeld*. Amsterdam, The Netherlands: Candide/Wrede Veldt.

Van Os, J., Marcelis, M., Germeys, I., Graven, S. & Delespaul, P. (2001) High expressed emotion: marker for a caring family? *Comprehensive Psychiatry*, 42, 504-507.

Vaughn, C.E. & Leff, J.P. (1976) The measurement of expressed emotion in the families of psychiatric patients. *British Journal of Social and Clinical Psychology*, 15, 157-165.

Wiersma, D., De Jong, A., Kraaijkamp, H.J.M. & Ormel, J. (1993) *GSB-II. De Groningse Sociale Beperkingen Schaal, tweede versie*. [The Groningen Social Disabilities Schedule]. Groningen, The Netherlands: University of Groningen, Department of Psychiatry.

Wieselgren, I.-M. & Lindström, L.H. (1996) A prospective 1-5 year outcome study in first-admitted and readmitted schizophrenic patients; relationship to heredity, premorbid adjustment, duration of disease and education level at index admission and neuroleptic treatment. *Acta Psychiatrica Scandinavica*, 93, 9-19.

Wing, J.K. (1966) Five-year outcome in early schizophrenia. *Proceedings of the Royal Society of Medicine*, 59, 17-18.

World Health Organization (1985) *A Procedure and Schedule for the Assessment of Disability in Patients with Severe Psychiatric Disorders (WHO Disability Assessment Schedule)*. Geneva, Switzerland: WHO.

Xiong, W., Phillips, M.R., Hu, X., Wang, R., Dai, Q., Kleinman, J. & Kleinman, A. (1994) Family-based intervention for schizophrenic patients in China. A randomised controlled trial. *British Journal of Psychiatry*, 165, 239-247.

Young, J.L., Zonana, H.V. & Shepler, L. (1986) Medication noncompliance in schizophrenia: codification and update. *Bulletin of the American Academy of Psychiatry and the Law*, 14, 105-122.

Zubin, J. (1972) Scientific models for psychopathology in the 1970's. *Seminars in Psychiatry*, 4, 283-296.

Zubin, J., Magaziner, J. & Steinhauer, S.R. (1983) The metamorphosis of schizophrenia: from chronicity to vulnerability. *Psychological Medicine*, 13, 551-571.

Zubin, J. & Spring, B. (1977) Vulnerability - a new view of schizophrenia. *Journal of Abnormal Psychology*, 86, 103-126.