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Early recovery and employment outcome 13 years after first episode psychosis

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GAF, Global Assessment of Function
FEP, first episode psychosis
SC, Strauss-Carpenter Outcome Scale
DDD, defined daily doses
SEK, Swedish kronor

ABSTRACT

175 cases of first episode psychosis were recruited to the Parachute project in 1996–97. The program offered highly available and continuous psychosocial support and a cautious use of antipsychotic medication for 5 years from inclusion.

Outcome-data for year 13 after inclusion, were retrieved from Swedish population registries on 161 of the original cases.

During the first year after inclusion the cohort improved in the scores of the Brief Psychiatric Rating Scale (BPRS) and Global Assessment of Function (GAF) to median levels that later remained rather stable. By month 12 the median GAF score was 65. 68% of the cases were in remission from psychotic symptoms as assessed with BPRS. 38% of the cases in remission and 60% not in remission had prescriptions of antipsychotic medication by month 12.

By year 13 after inclusion, 42% were in employment and 55% had any dispensation of antipsychotic medication. 70% of the cases with employment had no dispensations of antipsychotic medication.

In conclusion, Many first episode psychosis cases that were offered extensive psychosocial support and cautious use of antipsychotic medication had good early recovery and good late employment outcome.

1. Introduction

The long term outcome after a first episode psychosis (FEP) is heterogeneous (Austin et al., 2013; Henry et al., 2010; Jääskeläinen et al., 2013; Lally et al., 2017; Ten Velden Hegelstad et al., 2013). Some cases develop severely debilitating disorders with limited responce to antipsychotic medication, while some may discontinue antipsychotic medication after full recovery without relapses (Bowtell et al., 2017; Hegelstad et al., 2012; Landolt et al., 2016; Winton-brown et al., 2016). In a study of outcome 10 years after FEP in the OPUS project, 59% of the cases were in remission from psychotic symptoms, 60% had continuous antipsychotic medication, and 24% of the cases had ordinary employments (Wils et al., 2017).

Repeated studies have shown an association between discontinuation of antipsychotic medication after FEP and relapses in psychosis (Emsley et al., 2013; Wiersma et al., 1998). At the same time there are concerns about negative consequences of long term use of antipsychotic medication (Murray et al., 2016; Wunderink, 2017). Some researchers make the conclusion that the safest treatment strategy for all FEP cases is long term maintenance treatment with antipsychotic medication (Correll et al., 2018; Emsley, 2018; Fleischhacker, 2018), while others focus more on the chances for some cases to achieve a lasting recovery after discontinuation (Harrow and Jobe, 2018; Marder and Zito, 2018; Murray et al., 2016) and propose strategies where stepwise dose-reduction and discontinuation is an option in collaboration between patients and clinicians.

The Parachute project was based on a 5 years program for early intervention in first episode psychosis. Social and psychological support as well as other interventions, were continuously available for patients and relatives from small multidisciplinary FEP teams (Cullberg et al., 2002a), in a similar fashion to other FEP programs (Nordentoft et al., 2014; Ruggeri et al., 2015). In contrast to the protocols in many other programs, early antipsychotic medication was used cautiously, principally for positive symptoms with low doses and not longer than needed to achieve remission of psychotic symptoms.

In a 5 years outcome study of the Parachute cohort (Flyckt et al., 2006), 56% of the cases were judged to have a “good outcome”. Several predictors for the “good outcome” were identified including a high GAF score during the year before study admission, a higher education level, a higher GAF score at first admission, female gender, and a good social

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network.

In the current study we wanted to describe and analyse recovery and antipsychotic medication the first year after inclusion in the Parachute project, and late outcome 13 years after FEP in terms of employment, based on data from population registers.

2. Methods

2.1. Study design and patient recruitment

The Parachute project has previously been described in detail (Cullberg et al., 2002b). The principles of the program included intervention of all new FEP patients without delay, immediate and recurrent family meetings together with the patient, high accessibility to the multi-professional FEP team during a period of 5 years. Some of the clinics also offered access to small scale, homelike, low stimulus overnight facilities as a complement to standard inpatient care.

17 clinics throughout Sweden participated in the project, representing a catchment area of about 1.5 million inhabitants, or about one-sixth of Sweden's population. As no private care for early psychosis patients was available in Sweden, the patient cohort was believed to be rather complete regarding treated incidence of FEP. The collection of cases started 1 January 1996 and ended 31 December 1997 (24 months).

The inclusion procedure and criteria were as follows: Patients living in the catchment area, for the first time seeking psychiatric help for psychotic symptoms, age 18–45 years, and without a dominating substance abuse or a diagnosed brain disorder were identified as candidates. During the first week every candidate patient was diagnosed with a SCID-1 interview (Axis 1) according to DSM-IV – usually performed by a responsible psychiatrist. Cases with a diagnosis of Schizophrenia, Schizophreniform psychosis, Schizoaffective psychosis, Delusional disorder, Brief psychosis, Psychotic disorder Not Otherwise Specified, or Affective disorder with non-congruent psychosis were offered the opportunity to participate in the study.

253 patients were considered to fulfil criteria for FEP, corresponding to an incidence of FEP of 24.5 per 100,000 person-years in the population between 18 and 45 years of age (Cullberg et al., 2002b). Of these 175 accepted enrolment at baseline in the study (Fig. 1). Cases declining participation were found to have a higher age at FEP and fewer had DSM-IV 295 diagnoses, including schizophrenia (Cullberg et al., 2002b).

The first psychotic episodes of patients who agreed to participate in the study were retrospectively rediagnosed at the month 12 assessment.

Assessments were made on between 168 and 173 cases at the follow-up times up to months 12. The flow of cases in the study is presented in Fig. 1.

The program had a policy of using the lowest effective doses of antipsychotic medication “as needed” based on symptom severity and clinical judgement. Maintenance medication for the purpose of preventing relapse after remission from positive symptoms was not encouraged after the FEP. Antipsychotic polypharmacy was generally avoided. Attempts were made to avoid antipsychotic medication during the first 1–2 weeks if possible. Benzodiazepines were used for anxiety or insomnia during this period. Types and doses of antipsychotic medication were chosen based on clinical judgement. All patients were offered psychodynamically oriented psychotherapeutic support during the entire project stay.

After the 5 years project time, with access to the FEP teams, patients needing continuous care were referred to general psychiatric outpatient services, often with less accessibility to support.

2.2. Data collection and follow-up in the first year and years 3 and 5

All patients underwent a thorough somatic and psychiatric investigation, including a checklist of background variables and a series of rating scales covering symptoms and social functioning including BPRS (Silverstein et al., 1997), Strauss-Carpenter Outcome Scale (SC) (Strauss and Carpenter, 1972) and GAF (Endicott et al., 1976)). Cases were reassessed with BPRS and GAF after 2–4 weeks, 3 months, 1 year, 3 years and 5 years. Reassessments with the Strauss-Carpenter scale were made after 1, 3, and 5 years.

Remission from psychotic symptoms was estimated retrospectively based on the original BPRS assessments. The BPRS based criteria proposed by Andreasen et al. (2005), but without the prerequisite of 6 months stable state, were used. The variable thus represents a momentary state of remission from psychotic symptoms at the time of assessment.

Data on antipsychotic medication were retrieved from medical records for seven periods in the first 5 years (1st and 2nd-4th week, as well as the last week of the 3rd, 6th and 12th months and the last 2 weeks at the year 3 and 5 assessments). Dosages were converted to the

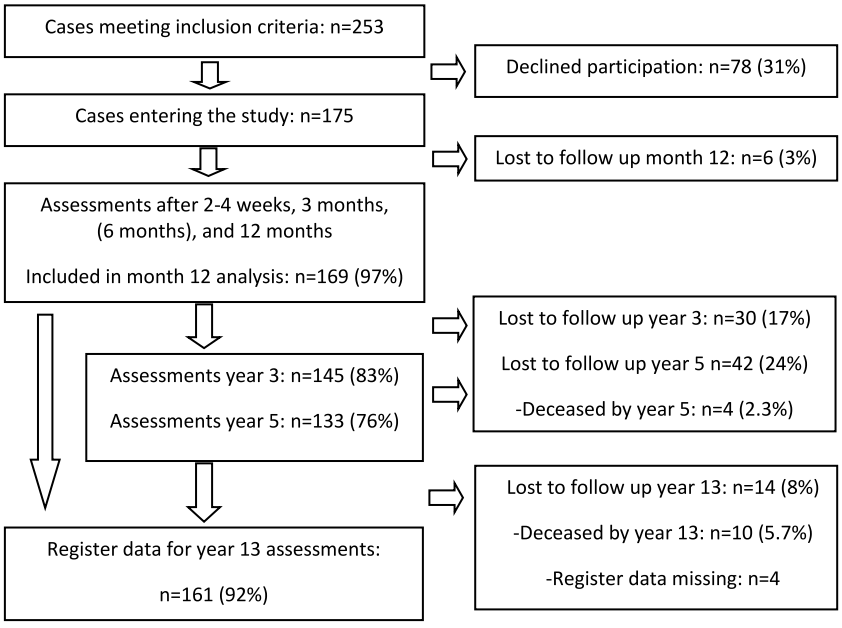

Fig. 1. Flow of participants in the Parachute project up to the year 13 follow-up.

"defined daily doses" (DDD) according to the WHO ATC/DDD Index (ATC/DDD Index [WWW Document], 2018), for the purpose of comparability with population register data, see below. Definitions of one DDD for some common antipsychotics are as follows: clozapine 300 mg, olanzapine 10 mg, risperidone 5 mg (2.7 mg for depot), haloperidol 8 mg (3.3 mg for depot), aripiprazole 15 mg, quetiapine 400 mg, paliperidone 6 mg (2.5 mg for depot).

Data on inpatient care were acquired from population registries for all analysed periods from study-inclusion until year 13.

2.3. Late outcome analyses

Data from population registries were used for late outcome analyses for the years 2009–2010. Data from 2009 was used for year 13 outcome analyses for cases included in the Parachute project in 1996 and data from 2010 for cases include in 1997.

The unique personal identity number assigned to each permanent resident in Sweden was used to link data from different registers:

Data on 172 cases were extracted from population registries. For 3 cases in the original study registry data could not be retrieved. For one case registry data was incomplete, probably due to international migration. 10 patients were recorded as dead prior to year 13 after inclusion. Population registry based analyses were made on 161 cases with complete records for the period 2009–2010.

Data from the following population registers were used in the study:

The In-patient Care Diagnoses Database from the Swedish National Board of Health and Welfare includes all individuals admitted to psychiatric or general hospitals (In-patient care diagnoses database, 2017; Ludvigsson et al., 2011) with dates for admission and discharge and ICD-10 diagnoses for the inpatient care.

The Causes of Death Database comprises information on all deaths of Swedish residents (Causes of death database, 2017).

The Swedish Prescribed Drug Database comprises information on all dispensed prescriptions in Sweden (Prescribed drugs database, 2017). However, it does not cover drugs administered at hospitals.

For analyses of antipsychotics, ACT codes N05A were used, with the exceptions of N05AN (lithium), N05AA02 (levomepromazine), N05AD03 (melperone), and N05AF03 (chlorprothixene) since these medications are usually used for other indications than psychotic symptoms.

Amounts of dispensed medication are reported in the register as number of "defined daily doses" (DDD) for every dispensation.

The Longitudinal integration database for health insurance and labor market studies (LISA) from Statistics Sweden includes data on income from employment, payments from sickness benefits and of student aides.

For the employment variable year 13, income above 100,000 Swedish kronor (SEK) (approximately 10,000 euro) was used as a cut-off for assignment as "employed".

2.4. Statistical methods

Descriptive analyses and logistic regression analyses were made with the R software (R: A language and environment for statistical computing, 2018). Significance levels for Odds Ratios were calculated based on Wald test statistics. Cases with missing data on a variable were excluded from that analysis.

The study design was reviewed and approved by the Ethical committee of the Karolinska Institute (dnr. 95–399).

3. Results

3.1. Description of the cohort

Demographic data for the cohort have previously been described (Cullberg et al., 2002b; Mattsson et al., 2007). 55% of the cases were males. Mean age at inclusion was 28.7 years. 10 cases had died before year 13, and were not included in the analyses (Fig. 1). Causes of death were suicide in 5 cases, overdoses of drugs in two cases (unclear if suicidal intentions), myocardial infarctions in two cases and pulmonary embolism in one case.

3.2. Primary diagnoses for the first episode psychosis

Retrospective SCID-1 interviews for the first episode psychosis were conducted at the month 12 assessment. The distribution of primary diagnoses for the 161 patients were as follows: 40 cases (25%) with Schizophrenia (DSM-IV 295.1/.2/.3/.6/.9), 13 cases (8%) with Schizophreniform disorder (DSM-IV 295.4), 11 cases (7%) with Schizoaffective disorder (DSM-IV 295.7), 17 cases (11%) with Delusional disorder (DSM-IV 297.1), 21 cases (13%) with Brief psychosis (DSM-IV 298.8), 30 cases (19%) with Psychosis NOS (DSM-IV 298.9), 12 cases (7%) with manic of bipolar disorder with non-congruent psychotic symptoms (DSM-IV 296.0/4/5/6/7/8), and 9 cases (6%) with major depression with non-congruent psychotic symptoms (DMS-IV 296.2/3).

3.3. Early follow up in the first year after inclusion

At inclusion the GAF scores were generally low and total scores on

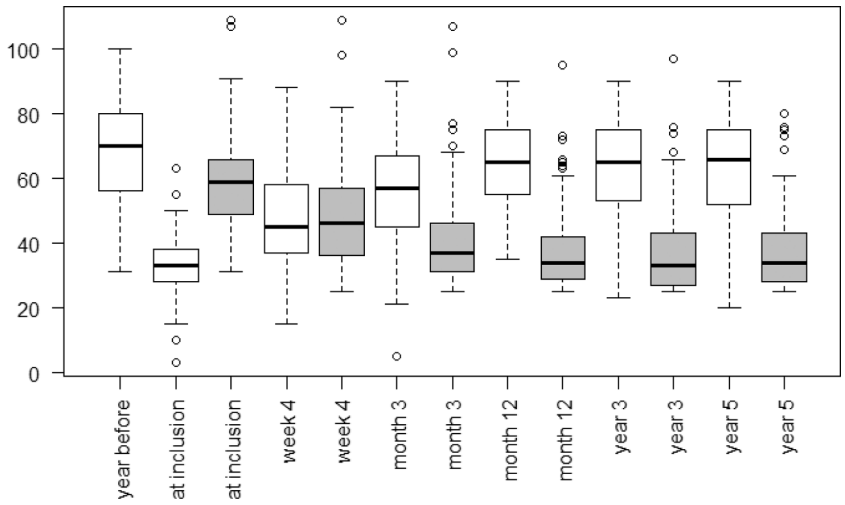

Fig. 2. Boxplot of temporal changes of GAF (white) and total BPRS (grey) scores. Maximal GAF the year before inclusion is also presented.

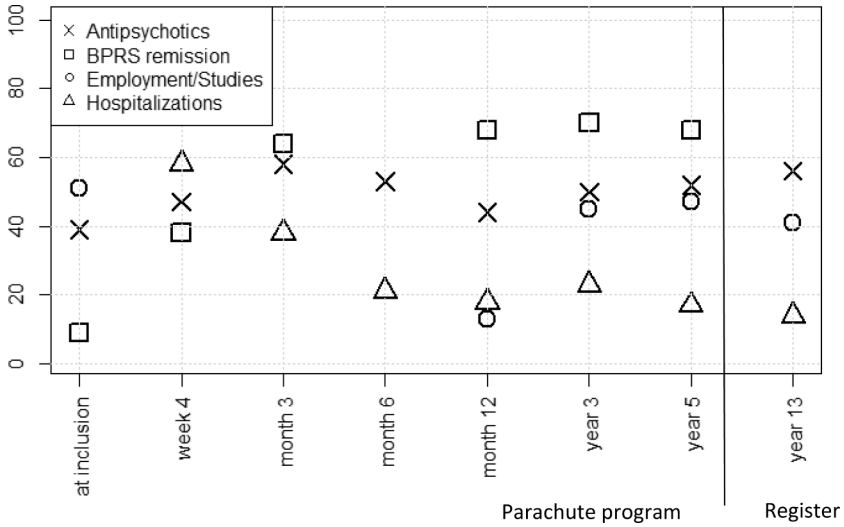

Fig. 3. Temporal changes in key characteristics. For time-points up to 5 years, cases with a prescription of antipsychotics the last 2 weeks before assessments were reported. For year 13, cases with any dispensation of antipsychotic medication during the year were reported, as extracted from population registries. The first point for inpatient care present the proportion of cases with any inpatient care in the period between inclusion and the following 4 weeks. In the first year the graph presents proportions of cases with psychiatric hospitalizations in the periods between time points. For the points at year 3, 5 and 13, cases with any psychiatric hospitalization the previous year were reported. Employment/studies were assessed with the Strauss-Carpenter scale up to year 5, and only cases in employment or regular education (almost) the whole previous year were reported. For year 13, cases with income of more than 100,000 SEK from employment were reported.

BPRS high as can be seen in Fig. 2. Already at the second assessment between week 2–4, the majority of cases had improvements in both measurements. The improvements in median GAF and BPRS scores continued during the first year, but thereafter, median levels and distributions were rather stable. By month 12 the median GAF score was 63 (25% and 75% quantiles: 51 and 72), and 68% of the cases were in BPRS based remission from psychotic symptoms.

The proportion of cases with hospitalizations decreased over the first year from a proportion of 58% in the first 4 weeks to 27% in the period between months 4–12 (Fig. 3). 16% of the cases had no hospitalization in the first year.

The proportion of cases using antipsychotics was around 40–60% at all assessment points in the first year (Fig. 3). By month 12, 42% of the cohort had a prescription of antipsychotic medication. Many patients were using antipsychotic medication for short periods. 13% of the cases with complete records on antipsychotic medication the first year had the medication at all the assessment points. 24% had no prescription of antipsychotic medication at any of the assessments the first year. 73% of the cases without any antipsychotics the first year, were in symptomatic remission by month 3.

The dosages of antipsychotics were similar between the assessments during the first year of follow up (Fig. 4). At the month 12 assessment, the median dosage was 0.40 DDD/day. 0.4 DDD/ day corresponds to for example 3.2 mg/day of haloperidol, 2 mg/day of risperidone, or 4 mg/day of olanzapine. The data on prescriptions of antipsychotics at inclusion were incomplete and difficult to calculate due to a higher level of acute and temporal medication in cases with any antipsychotics.

By month 12, the most common antipsychotic medications were risperidone in 34% of cases, olanzapine in 17%, perfenazine in 17% and flupentixol in 15%. 8% of the cases had more than one antipsychotic.

Of the 64 cases with a schizophrenia related syndrome (DSM-IV 295), 40 cases (62%) had a prescription of antipsychotics and 34 (56%) were in symptomatic remission at the month 12 assessments.

3.4. Outcome years 3 and 5 after inclusion

Outcome data for the years 3 and 5 are also presented in the figures. The distributions of GAF and BPRS scores (Fig. 2) and of amounts of antipsychotics prescribed (Fig. 4) were similar to year 1. The proportions of cases with antipsychotic medications and with hospitalizations were similar to year 1(Fig. 3). Data on outcome years 3 and 5 are not further elaborated in the current paper.

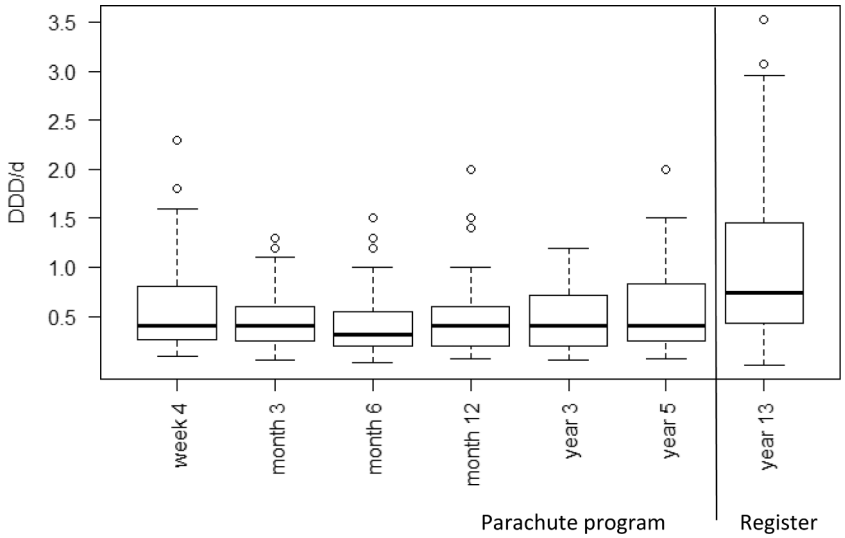

Fig. 4. Boxplots of dosages of antipsychotic medication, presented as DDD/ day. For time-points up to 5 years daily dosages the last 2 weeks before assessments were reported. For year 13 daily dosages were calculated based on all dispensations of antipsychotic medication during the year as extracted from population registries.

Table 1
Associations between possible early predictors and outcome year 13 after inclusion. Complete data were available for 161 cases. Cases with incomes of more than 100 000 SEK from employment during year 13 were categorized as employed. Retrospective primary diagnoses for the FEP were dichotomized into "Schizophrenia related syndromes" for schizophrenia, schizophreniform disorder and schizoaffective disorder, and "Non-schizophrenia syndromes" for delusional disorder, brief psychosis and psychosis NOS. OR = Odds Ratio.

	Cohort	Any antipsychotics year 13	Employment year 13
Cohort	$n = 161$	55% (89 av 161)	42% (67 av 161)
High school exam	78%, (122 of 157)	51%, (62 of 122) OR = 0.41	48%, (58 of 122) OR = 3.62
Not High school exam	22%, (35 of 157)	71%, (25 of 35) OR = 2.42 $p = 0.034$	20%, (7 of 35) OR = 0.28 $p = 0.0051$
Maximal GAF the year before FEP < 70	47%, (74 of 156)	68%, (50 of 74) OR = 2.66	23%, (17 of 74) OR = 0.20
Maximal GAF the year before FEP ≥ 70	53%, (82 of 156)	44%, (36 of 82) OR = 0.38 $p = 0.0033$	60%, (49 of 82) OR = 4.98 $p < 0.001$
Age at FEP ≤ 25 years	37%, (59 of 159)	59%, (35 of 59) OR = 1.29	29%, (17 of 59) OR = 0.42
Age at FEP > 25 years	63%, (100 of 159)	53%, (53 of 100) OR = 0.77 $p = 0.44$	49%, (49 of 100) OR = 2.37 $p = 0.014$
Schizophrenia related syndromes (DSM-IV 295)	40%, (64 of 161)	72%, (46 of 64) OR = 3.21	23%, (15 of 64) OR = 0.26
Non-schizophrenia syndromes (not DSM-IV 295)	60%, (97 of 161)	44%, (43 of 97) OR = 0.31 $p < 0.001$	54%, (52 of 97) OR = 3.77 $p < 0.001$
Symptomatic remission at month 12	68%, (101 of 148)	49%, (49 of 101) OR = 0.32	50%, (50 of 101) OR = 2.86
Not symptomatic remission at month 12	32%, (47 of 148)	74%, (35 of 47) OR = 3.1 $p = 0.0037$	26%, (12 of 47) OR = 0.35 $p = 0.007$

3.5. Late outcome in the year 13 after inclusion based on population registries

89 of 161 cases (55%) had any dispensed prescription of antipsychotics year 13 (Table 1). Compared to the median levels and distributions in the first 5 years of follow-up, the dosages were higher in year 13, with a median level of 0.73 DDD/day, but with a wider distribution (Fig. 4). 0.7 DDD/day corresponds to for example 3.5 mg of risperidone or 7 mg of olanzapine. 21 cases (13%) had any hospitalization in year 13. Median stay in hospital was 21 days (25% and 75% quantiles: 14, 37).

86 cases (53%) had any income and 67 cases (42%) had an income above 100 000 SEK year 13 (Table 1, Fig. 3).

47 of the cases with employment year 13 did not have any dispensation of antipsychotics year 13 (70% of the cases with employment and 29% of the cohort).

Employment year 13 was significantly associated with a higher educational level at FEP, with a higher maximal GAF the year before FEP, with a higher age at FEP, with not having a schizophrenia related syndrome at FEP, and with symptomatic remission by month 12 after FEP (Table 1).

The same factors, with the exception of age, had a significant association with not having any antipsychotic medication year 13 (Table 1).

17 of 26 cases (65%) without any antipsychotic medication in the first year had no dispensation of antipsychotics in the year 13. 10 of the 17 cases with no antipsychotics had employments year 13.

56 of 91 cases (62%) without antipsychotic medication by month 12 had no dispensation of antipsychotics in the year 13. 36 of the 56 cases without antipsychotic medicine both by month 12 and year 13 had employment year 13.

4. Discussion

To our knowledge this is the first study of long-term outcome after FEP in a reasonably complete population of patients treated with intense psychosocial support and with early cautious antipsychotic medication "as needed". The drop-out rate year 13 after inclusion is minimal due to the methodology of data acquisition by population registers.

A majority of the cases were in remission from psychotic symptoms by months 3 and 12, in line with results in other cohorts (Lally et al., 2017; Lieberman et al., 1993). The use of antipsychotic medication was cautious throughout the first year and also later, as reflected in the low proportion of cases with antipsychotic medication at any assessment in the first five years, by the rather large proportion of cases without any antipsychotic medication in the first year, and by the low dosages used, as compared to some other FEP cohorts (Kahn et al., 2008; Strålin and Hetta, 2018).

In the long-term follow up year 13, there was a high proportion of cases with employment, indicating that a large part of FEP patients has a potential for recovery to a substantial extent, in line with several other studies (Bond et al., 2015; Henry et al., 2010; Wils et al., 2017). A majority of the cases in employment did not have any dispensations of antipsychotic medication in the year 13.

The retrospective primary diagnoses by month 12 had a high prospective diagnostic stability (Rahm and Cullberg, 2007). A significantly higher proportion of cases with schizophrenia related syndromes (DSM-IV 295) had prescriptions of antipsychotic medication by month 12. Not surprisingly, a diagnosis of a schizophrenia related syndrome by month 12 was associated with a less favourable employment outcome year 13. Good employment outcome was more generally predicted by factors representing good premorbid function and early remission from psychotic symptoms, including educational level, maximal GAF the year before inclusion, age at FEP, and symptomatic remission by month 12. Similar associations have previously been found in other studies of recovery after FEP (Santesteban-Echarri et al., 2018).

24% of the cases in the cohort did not have any prescription of antipsychotic medication in the first year. The follow up data indicate that some of these cases recovered from acute psychosis without antipsychotic medication and were in employment by year 13, but also that some cases had recurrent psychotic symptoms at assessments, and had dispensations of antipsychotic medications by year 13. The outcome illustrates that a smaller part of FEP cases can recover without any antipsychotic medication (Conus et al., 2017).

Dosages of antipsychotic medication were rather stable at low median levels in the first 5 years when the early intervention program was running, but higher in the year 13, although the distribution was wider. The principles and availability of care and support in later years were not controlled for, and may have varied between locations. It is possible that the termination of the early intervention program, with the high availability of support and psychiatric consultations,

contributed to increased doses in some cases. A similar trend was noted in the OPUS project (Bertelsen et al., 2008).

With a policy of a cautious use of antipsychotic medication in an early phase of the disorder there may be an increased risk for relapses (Bowtell et al., 2017; Winton-brown et al., 2016). On a group level there were no signs of worse outcomes though. The rate of hospitalizations in the Parachute cohort was not high compared to similar cohorts (Cullberg et al., 2006; Strålin and Hetta, 2018), the number of deaths in the study, both suicides and other deaths, were similar to the mortality in other psychosis cohorts (Nordentoft et al., 2013; Strålin and Hetta, 2018), and the rates of late employment were actually high. The high availability to support and to psychiatric consultations may have ameliorated negative consequences of relapses by managing fast re-initiation of antipsychotic medication when needed in many cases. The frequency of relapse is known to be high also in cohorts with recommendations of maintenance treatments (Winton-brown et al., 2016). The current study thus does not support views of general deleterious long-term effects with a cautious use of antipsychotic medication after FEP.

A limitation in the study was that cases with severe drug and alcohol abuse were not included in the study.

The measures for employment and antipsychotic medication year 13 after inclusion were different from the measures in the first 5 years as explained under Methods. It is therefore necessary to be cautious in drawing conclusions from the differences in variables on medication and employment over time to the late outcome year 13.

There was a selection of cases declining participation in the study. A previous analysis of the 78 cases declining participation found that the median age was higher in the drop-out group and that fewer had a schizophrenia related diagnosis (DSM-IV 295) (Cullberg et al., 2002b), favouring a somewhat better prognosis in the drop-out group.

In conclusion, the good employment outcome in the Parachute project suggests that the principles of the FEP program may have contributed to a good recovery for many cases.

Clinicians should be aware of the potentials for a good employment outcome for many FEP cases, particularly cases with good premorbid function and early remission from psychotic symptoms. The study suggests that many FEP patients may benefit from support for employment by methods such as “Individual Placement and support” (Bond et al., 2015).

The study also suggests that FEP patients may benefit from a cautious use of antipsychotic medication in an early phase, when needed to treat symptoms, and that many may terminate treatment early after full symptomatic remission without a high risk for a deteriorating course of a psychotic disorder. More studies are needed to improve the knowledge of predictors for which patients in an early phase will need long term antipsychotic medication, and which may successfully terminate or even not start antipsychotic treatment (Correll et al., 2018).

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