Long-term antipsychotic use and its association with outcomes in schizophrenia - the Northern Finland Birth Cohort 1966

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A B S T R A C T

Background: Due to the paucity of previous studies, we wanted to elucidate the pharmacoepidemiology of antipsychotics in schizophrenia in a general population sample, and the association between long-term antipsychotic use and outcomes.
Methods: The sample included 53 schizophrenia subjects from the Northern Finland Birth Cohort 1966 with at least ten years of follow-up (mean 18.6 years since illness onset). Data on lifetime medication and outcomes (remission, Clinical Global Impression [CGI], Social and Occupational Functioning Assessment Scale [SOFAS]) were collected from medical records, interviews, and national registers.
Results: During the first two years 22 (42%), between two to five years 17 (32%), and between five to ten years 14 (26%) subjects had used antipsychotics less than half of the time. Drug-free periods became rarer during the follow-up. The mean lifetime daily dose of antipsychotics was 319 mg in chlorpromazine equivalents. A high lifetime average and cumulative dose and antipsychotic polypharmacy were associated with a poorer outcome in all measures, whereas having no drug-free periods was associated with a better SOFAS score and a low proportion of time on antipsychotics with a better CGI score.
Conclusions: In our population-based sample, the use of antipsychotics increased during the first five years of illness and was relatively stable after that. Our results suggest that both low dose and proportion of use, and having no drug-free periods, are associated with better outcomes, which concords with current treatment recommendations and algorithms. High long-term doses and polypharmacy may relate to poor outcomes.

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1. Introduction

The effectiveness of antipsychotics on positive symptoms and relapse prevention in schizophrenia has been shown [1,2], but harmful side effects are common [1,3]. Antipsychotics are often used as a long-term maintenance treatment, although the clinical guidelines, such as those on dosing, are not consistent [4].

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The effectiveness of antipsychotics in the long-term has been questioned [5], and long-term use has even been suggested to be an iatrogenic cause of chronicity of schizophrenia [6,7]. This was not supported by the systematic review by Sohler et al. [8], in which they concluded that the published data was inadequate to answer the question about long-term treatment with antipsychotic medication causing harm. In consideration of neuroprotection versus neurotoxicity, relapses may be harmful [9]. On the other hand, imaging studies have suggested that some of the volume alterations shown in schizophrenia may be associated with antipsychotic treatment [10].

In the multinational incident cohorts of the World Health Organization, an average of 25.5% of patients with schizophrenic

psychosis had not used antipsychotic medication during the last two years of the 15-year follow-up [11]. Earlier studies show that continuous medication after acute treatment decreases the risk of relapse during first two years, compared to medication withdrawal or intermittent antipsychotic treatment [5,12–14]. Long-term effects of dose lowering or discontinuation of antipsychotics are not fully known, because there is a lack of studies with a follow-up longer than two years. Wunderink et al. [15] stated that early dose reduction or discontinuation of antipsychotics in remitted first-episode psychosis shows superior long-term functioning after seven years compared with maintenance treatment. However, these patients were at higher relapse risk during the first two years. In the longitudinal study by Harrow et al. [16–18], non-medicated individuals with schizophrenia had favorable outcomes compared to medicated ones. These results suggest different effects of antipsychotic treatment and non-medication or discontinuation in the short term and long-term.

Antipsychotic polypharmacy (APP) is common in the treatment of schizophrenia [19,20]. Evidence of the effectiveness of APP is lacking, even though APP may be effective in certain circumstances compared to monotherapy [21–23]. APP is associated with greater prevalence of adverse effects and increased costs [24], but no association between APP and increased mortality was found [25].

In summary, more information on long-term antipsychotic treatment with its benefits and drawbacks, and on antipsychotic non-medication or discontinuation, is needed [8]. In earlier studies within the Northern Finland Birth Cohort 1966 (NFBC 1966), we found that non-medicated subjects had favorable clinical outcomes [26], that length of non-medication was associated with increased gray matter volume [27], and that use of antipsychotics was associated with higher symptom scores and a higher number of hospital days [28].

Here we will study the associations between long-term antipsychotic use and outcomes within NFBC 1966. Our naturalistic, population-based sample offers an opportunity to explore the long-term use of antipsychotic medication, which is not possible in randomized controlled trials [29].

1.1. Aims

Our aim was to describe how individuals with schizophrenia use antipsychotics in the long-term, with a minimum of 10 years of illness, and to study the association between different characteristics of long-term antipsychotic use and outcomes.

2. Methods

2.1. The Northern Finland Birth Cohort 1966

The NFBC 1966 is an unselected, general population birth cohort based on 12,058 children born in the provinces of Lapland and Oulu [30]. The study design is approved by the local Ethics Committee. This study is based on a follow-up of the NFBC 1966 on psychosis, performed in 2008–2011, at approximately 43 years of age [28].

2.2. Case description

The principal source of hospitalization data was the Care Register for Health Care (hereafter the Care Register) covering all hospitals and health centers nationwide. The following information was used: psychosis diagnosis by 2008 according to the Care Register; indications of psychosis in the register data (i.e. sick leave [data −1999] or disability pension due to psychosis [−2000], or a right to reimbursement for psychoactive medication [−2005]); or self-reported psychosis or current high-dose antipsychotic use

(over 300 mg chlorpromazine equivalents) at 31 years of age in the questionnaire.

2.2.1. Sample

Out of 258 invited persons, 175 had a schizophrenia spectrum disorder diagnosis. Out of 69 participants, 53 had detailed information on long-term antipsychotic medication and a requested follow-up time lasting at least 10 years following the onset of illness. The formation of the study sample is shown in Fig. 1. Written informed consent and permission to collect medical data were obtained after they had been given a complete description of the study.

A Structured Clinical interview for DSM Axis I Disorders (SCID-I) interview leading to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) lifetime diagnoses was performed at the follow-up. The participants' diagnoses were schizophrenia ($n = 47$), delusional disorder ($n = 2$), and schizoaffective disorder ($n = 4$). The diagnoses of non-participants and excluded subjects are given in Fig. 1.

The participants did not differ from the non-participants ($n = 106$) and those excluded due to missing data on medication ($n = 8$) or short follow-up time ($n = 8$) in terms of gender or diagnosis. The participants had illness onset at a younger age than the non-participants (23.9 vs. 28.3 years, $P < 0.001$), and they had more hospital treatment days due to psychiatric disorders (545 vs. 360, $P = 0.045$ [for logarithmic transformations]). When adjusted for the onset age, the difference in treatment days did not remain significant.

2.3. Data on medication

Data on lifetime antipsychotic medication use were collected during 2008–2012 using all available hospital and outpatient records. The data were completed using the interviews conducted during the follow-up and the register of the Social Insurance Institution of Finland on psychoactive medications consumed during 1997. The medical records were obtained based on information from subjects' treatment facilities, which we received from the Care Register. If the subject had no information in the Care Register, medical records were requested from outpatient facilities. All medical records were reviewed to record the antipsychotic agent, dosage, and the time period the medication was used. The notifications in the medical records concerning the use of medication, such as whether a subject had hidden drugs or reported not using them, were taken into account while gathering data on medications. See the Supplementary Table for an exact description of the antipsychotics and chlorpromazine equivalents used. The data on antipsychotic medication has been used in earlier studies with shorter periods of follow-up [27,31,32].

2.4. Variables

2.4.1. Background variables

2.4.1.1. Sex. Males versus females.

2.4.1.2. Level of education. Low = 9 years of non-vocational with a lower level of vocational education; middle = 9 years of non-vocational with a higher level of vocational education, or 12 years of non-vocational with a lower level of vocational education; and high = 12 years of non-vocational with a higher level of vocational education. Information from the follow-up questionnaire.

2.4.1.3. Marital status. Married or cohabiting versus others at the time of follow-up assessment. Information from the follow-up questionnaire.
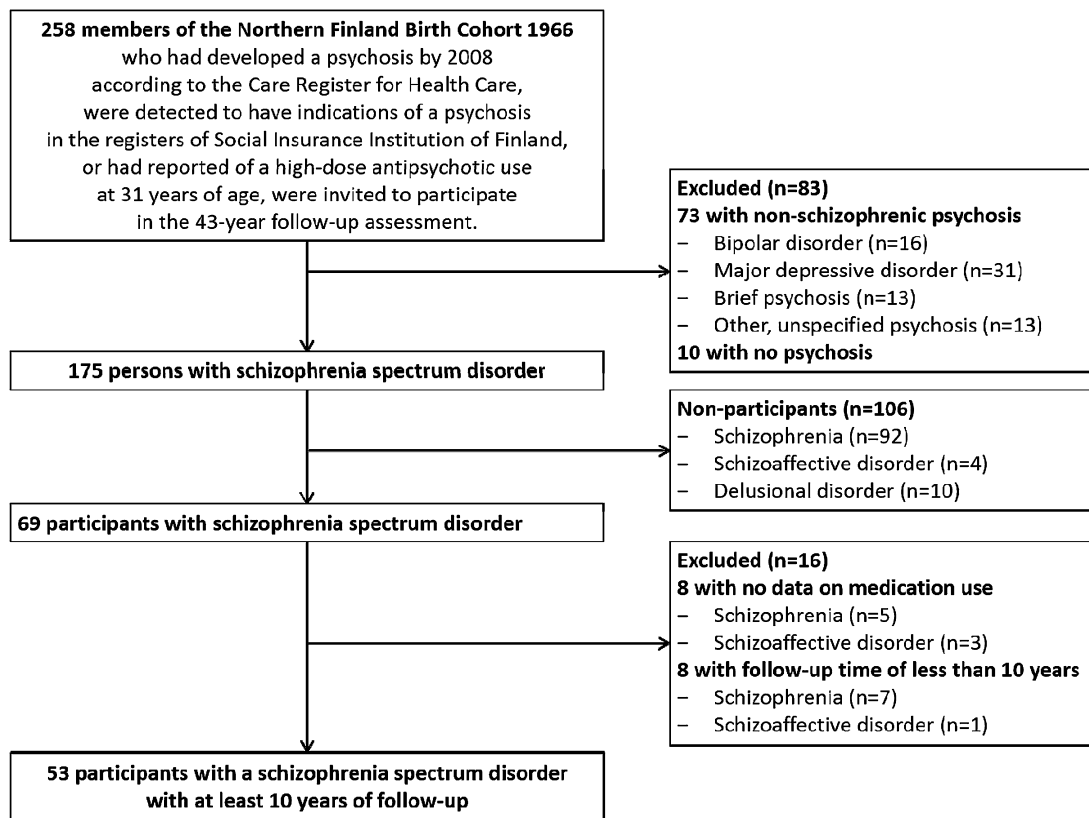
Fig. 1. The formation of the study sample and the ICD-10 diagnoses of the non-participants.

2.4.1.4. Parental psychosis. Parents' psychosis diagnosis in 1972–2012. Information from the Care Register.

2.4.1.5. Onset age. Ascertained from the medical records and health registers, and defined as the age when the first psychotic symptoms appeared [33].

2.4.1.6. Duration of follow-up. Duration of follow-up from the beginning of the treatment to the follow-up assessment varied from 10.3 to 26.7 years (mean 18.6, SD 4.8 years).

2.4.1.7. Psychiatric hospitalization. Cumulative number of hospital treatment days and episodes due to any psychiatric disorder until the follow-up. Evaluated using the Care Register.

2.4.1.8. Psychiatric comorbidities. Substance use disorder or any other non-psychotic disorder (depressive, bipolar, anxiety, eating, or other disorder) until the end of follow-up. Information from the registers specified in the case description.

2.4.1.9. Somatic comorbidities. Somatic comorbidities included pulmonary diseases, cardiovascular diseases, endocrinological diseases, and others. Information from the follow-up questionnaire.

2.4.2. Medication variables
2.4.2.1. Long-term cumulative antipsychotic use. Long-term cumulative antipsychotic use during the follow-up, expressed as dose-years of a daily dose of 100 mg chlorpromazine [27,34], was calculated as chlorpromazine equivalent (mg) multiplied by the time on dose (years).

2.4.2.2. Proportion of time with medication since onset of treatment. Using the information on the days when subjects were on

antipsychotic treatment, they were divided into three groups based on the regularity of daily antipsychotic use ($< 50\%$, 50–95%, $> 95\%$ of the time). The cut-offs were selected based on the distribution of the data. In order to study the proportion of antipsychotic use in different phases of illness, we did the above-mentioned division for the first two years, two to five years, and five to ten years after the onset of illness, and for the whole follow-up time. Additionally, the proportions of time using typical or atypical antipsychotics, or both, for the whole follow-up were calculated.

2.4.2.3. Average dose when medicated. The average daily dose in chlorpromazine equivalents when using antipsychotics was classified as low (< 300 mg) or high (≥ 300 mg).

2.4.2.4. Drug-free periods. Drug-free periods lasting for at least 30 days during the follow-up time (yes or no).

2.4.2.5. Antipsychotic polypharmacy (APP). Subjects were divided into three groups based on the proportion of time on APP, when using antipsychotic medication ($< 5\%$, 5–40%, $> 40\%$). The cut-offs were selected based on the distribution of the data.

2.4.3. Outcome variables
2.4.3.1. Functioning. The Social and Occupational Functioning Assessment Scale (SOFAS) [35] uses a scale of 0–100, with higher scores reflecting better functioning. Subjects were divided into two groups: 0–60 points meaning impairments, and over 60 points meaning relatively good functioning.

2.4.3.2. Symptomatology and remission. Symptoms during the preceding week were measured during the interview using the Positive and Negative Syndrome Scale (PANSS) [36], which measures the number and extent of psychopathological

symptoms, especially psychotic ones. Subjects were divided into remission groups based on the criteria of Andreasen et al. [37], with the exception that, as the symptoms had been assessed only once, the duration of remission criterion of six months was not applied. The symptom criteria for remission are: maximum scores of 3 in PANSS items P1, P2, P3, N1, N4, N6, G5, and G9.

2.4.3.3. Clinical outcome. Clinical Global Impression (CGI) [38] describes the severity of illness on a scale from 1 to 7, where 1 = healthy and 7 = very ill. In the follow-up interview, subjects were divided into two groups: 4–7 points meaning at least moderately ill (poor clinical outcome), and 1–3 points meaning at most mildly ill (good clinical outcome).

2.5. Statistical analyses

The participants were compared with the non-participants using a Chi² test, an independent samples *t*-test, or the analysis of variance. The illness-related background variables were compared between medication groups using a Chi² test, a Kruskal–Wallis H test, or the one-way analysis of variance. A Chi² test or Mann–Whitney's *U* test was used to study the effect of medication variables on outcome variables. A Benjamini–Hochberg procedure was used to correct for multiple comparisons. If the association remained significant, a logistic regression analysis was used to control for selected confounding factors, such as for psychiatric hospital days and length of follow-up, which were used as proxy variables for the severity of illness. Long-term dose-years were used to control for total antipsychotic exposure. The logarithmic transformations of the hospital treatment days and the dose-years were used. *P*-values of less than 0.05 were considered statistically significant. IBM SPSS Statistics 22.0 was used.

3. Results

3.1. Descriptive results of medication use

At the follow-up interview, 43 (81%) subjects used antipsychotics. During the first two years (from the illness onset), 22 (42%) subjects had used antipsychotics less than 50% of the time, between two to five years 17 (32%), between five to ten years 14 (26%), and during the whole follow-up 13 (25%). Males had used antipsychotics on average 69% (median 86%) and females 77% (median 88%) of the follow-up time. The mean proportions of time with exposure to antipsychotics during the whole follow-up were 55.5% (SD 35.9) for typical and 35.2% (SD 35.6) for atypical antipsychotics, and 9.9% (SD 19.0) for both. Forty-four (83%) subjects had drug-free periods lasting at least 30 days; 35 (66%)

during the first two years of the follow-up, 33 (62%) between two to five years, and 23 (43%) after five years.

Long-term cumulative antipsychotic use in the whole follow-up varied from 0 to 252 (mean 53, median 32) in dose-years. Only one subject was without antipsychotic treatment during the whole follow-up. The mean dose when using antipsychotics within the whole sample was 319 mg in chlorpromazine equivalents (males, mean 350 mg, median 290 mg, range 0–1060 mg; females, 281 mg, median 246 mg, range 49–847 mg). The proportion of antipsychotic use and the mean doses when using medication during the ten-year follow-up after onset of illness are shown in Fig. 2. Mean dose increased from approximately 150 to 250 chlorpromazine equivalents. The proportion of those using antipsychotics was lowest after six months (53%) and was relatively stable after five years (70%).

3.1.1. Background factors by the proportion of medication use

Those who used antipsychotics less than 50% of the time were more often males, had a higher level of education, were more often married or in cohabitation, had become ill at an older age, and had better scores in PANSS at the follow-up assessment (Table 1). They had the smallest number of treatment episodes and treatment days, whereas those who used antipsychotics between 50 and 95% of the time had the most.

3.1.2. Psychiatric and somatic comorbidities

Altogether, 12 subjects had been diagnosed with depression, 4 with bipolar disorder, 7 with anxiety disorder, 9 with harmful alcohol use or dependence, 9 with any substance use, and 1 with eating disorder. Altogether, 10 subjects reported having somatic comorbidities: pulmonary diseases (*n* = 3), cardiovascular diseases (*n* = 2), endocrinological diseases (*n* = 3), myasthenia gravis (*n* = 1), and Crohn's disease (*n* = 1).

3.2. Association between medication use and outcome

3.2.1. Proportion of medication use

Those who used antipsychotics less than 50% of the time had a better clinical outcome (*P* = 0.022) at the follow-up compared to those who used antipsychotics more than 50% of the time (Table 2).

3.2.2. Average dose when medicated

Subjects who had used less than 300 mg of antipsychotic medication daily had a better outcome in all measures (SOFAS, *P* = 0.013; remission, *P* = 0.026; and CGI, *P* = 0.050) compared to those who had used 300 mg or more (Table 2). In SOFAS, the statistical significance remained after a Benjamini–Hochberg correction (*P* = 0.039) and when adjusted for the treatment days and the length of the follow-up (*P* = 0.041 and *P* = 0.038,
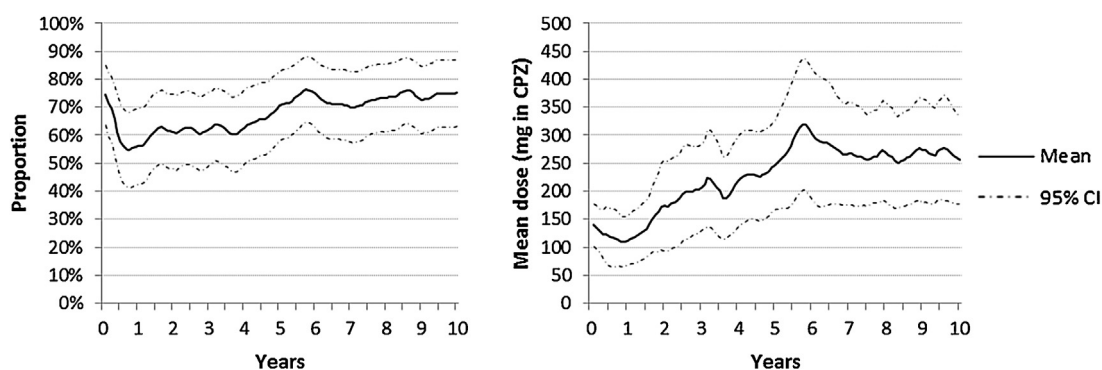

Fig. 2. Mean antipsychotic dose (mg in chlorpromazine equivalents) and proportion (%) of antipsychotic use during ten-year follow-up after onset of illness. Lines are smoothed using 5-month moving averages.

Table 1
Background factors by the proportion of antipsychotic medication use in the long-term.

	Proportion of long-term antipsychotic use				
	Total	< 50% ($n = 13$)	50–95% ($n = 22$)	> 95% ($n = 18$)	P-value
Sex, n (%)					0.53[a]
Male	30 (57%)	9 (69%)	11 (50%)	10 (56%)	
Female	23 (43%)	4 (31%)	11 (50%)	8 (44%)	
Education, n (%)					0.47[a]
Low	30 (58%)	6 (46%)	13 (59%)	11 (64%)	
Middle	11 (21%)	2 (15%)	6 (27%)	3 (18%)	
High	11 (21%)	5 (39%)	3 (14%)	3 (18%)	
Marital status, n (%)					0.37[a]
Married or in cohabitation	17 (32%)	6 (46%)	5 (23%)	6 (33%)	
Unmarried, divorced or widowed	36 (68%)	7 (54%)	17 (77%)	12 (67%)	
Parental psychosis, n (%)					0.27[a]
Yes	8 (15%)	3 (23%)	1 (4.5%)	4 (22%)	
No	45 (85%)	10 (77%)	21 (95.5%)	14 (78%)	
Diagnosis, n (%)					0.64[a]
Schizophrenia	47 (89%)	11 (85%)	19 (86%)	17 (94%)	
Other schizophrenia spectrum disorder	6 (11%)	2 (15%)	3 (14%)	1 (6%)	
Onset age, mean (SD)	24.0 (4.9)	26.2 (3.5)	24.1 (5.1)	22.3 (5.1)	0.090[b]
Duration of follow-up, mean (SD)	18.6 (4.8)	16.0 (3.8)	18.3 (4.8)	20.8 (4.5)	0.019[b]
Psychiatric treatment, median (IQR)					
Episodes	7 (3–13.5)	3 (1.5–12)	11 (6–19)	5.5 (3–12)	0.035[c]
Days	219 (90–715)	82 (28–258)	372 (184–926)	235 (91–989)	0.016[c]
Long-term dose-years, median (IQR)	32.2 (14–77)	3.3 (1–11)	33.1 (19–74)	74.3 (4–118)	< 0.001[c]
PANSS, total score, mean (SD)	69.6 (25.4)	55.5 (17.0)	71.7 (23.1)	78.0 (30.2)[d]	0.048[b]

PANSS: Positive and Negative Syndrome Scale; CGI: Clinical Global Impression Scale; SOFAS: Social and Occupational Functioning Assessment Scale; SD: standard deviation; IQR: interquartile range.
[a] Significance from Chi^2 test.
[b] Significance from One-way ANOVA.
[c] Significance from Kruskal–Wallis H test.
[d] $n = 16$.

respectively), but not when adjusted for the total dose-years ($P = 0.20$). The proportion of antipsychotic use and the average dose when medicated during the first ten years of the follow-up, by functioning, remission, and clinical outcome, are shown in Fig. 3. The average dose was stable among those with good outcomes. The average dose increased during the follow-up among those with poor outcomes.

3.2.3. Drug-free periods, polypharmacy, and cumulative use

Having no drug-free periods (lasting at least 30 days) was associated with better functioning ($P = 0.048$) (Table 2). APP and long-term cumulative antipsychotic use were associated with poorer outcomes in all measures (Table 2), including when adjusted for the treatment days and the length of the follow-up. When adjusted for the total dose-years, APP remained

Table 2
The long-term use of antipsychotic medication and its association with outcome at the age of 43 years.

	Functioning (SOFAS)		P-value	Remission[a]		P-value	Clinical outcome (CGI)		P-value
	Impairments ($n = 38$)	Relatively good ($n = 15$)		No ($n = 35$)	Yes ($n = 15$)		Poor ($n = 40$)	Good ($n = 13$)	
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Proportion of long-term antipsychotic use, n (%)			0.23[b]			0.096[b]			0.022[b]
< 50%	7 (54%)	6 (46%)		6 (46%)	7 (54%)		6 (46%)	7 (54%)	
50–95%	18 (82%)	4 (18%)		18 (82%)	4 (18%)		19 (86%)	3 (14%)	
> 95%	13 (72%)	5 (28%)		11 (73%)	4 (27%)		15 (83%)	3 (17%)	
Average dose,[c] n (%)			0.013[b,g]			0.026[b]			0.050[b]
< 300 CPZ	18 (58%)	13 (42%)		18 (58%)	13 (42%)		20 (65%)	11 (35%)	
≥ 300 CPZ	20 (91%)	2 (9%)		17 (81%)	2 (11%)		20 (91%)	2 (9%)	
Drug-free periods,[d] n (%)			0.048[b]			0.20[b]			0.66[b]
No	4 (44%)	5 (56%)		4 (50%)	4 (50%)		6 (67%)	3 (33%)	
Yes	34 (79%)	9 (21%)		31 (76%)	10 (24%)		34 (79%)	9 (21%)	
Antipsychotic polypharmacy,[e] n (%)			0.002[b,g]			0.003[b,g]			0.002[b,g]
< 5%	11 (48%)	12 (52%)		11 (48%)	12 (52%)		12 (52%)	11 (48%)	
5–40%	13 (81%)	3 (19%)		12 (80%)	3 (20%)		14 (87%)	2 (13%)	
> 40%	14 (100%)	0 (0%)		12 (100%)	0 (0%)		14 (100%)	0 (0%)	
Long-term dose-years, median (IQR)	41 (19–96)	19 (2–27)	0.004[f,g]	36 (19–85)	11 (1–30)	0.003[f,g]	41 (21–92)	9 (1–23)	0.001[f,g]

SOFAS: Social and Occupational Functioning Assessment Scale (0–100; under 60 points meaning impairment; 60 points or more meaning relatively good); CGI: Clinical Global Impression scale (1–7; 4–7 meaning clinically poor; 1–3 meaning clinically good).
[a] Remission criteria: maximum scores of 3 in PANSS items P1, P2, P3, N1, N4, N6, G5, and G9.
[b] Significance from Chi^2 test.
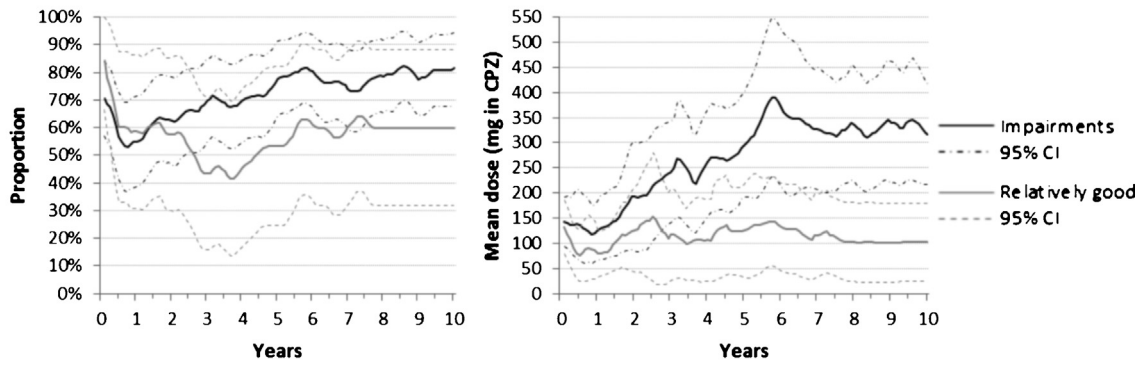[c] Average daily dose in chlorpromazine equivalents (CPZ) when using antipsychotic medication.
[d] Any drug-free period lasting at least 30 days.
[e] Proportion of antipsychotic polypharmacy when using antipsychotic medication.
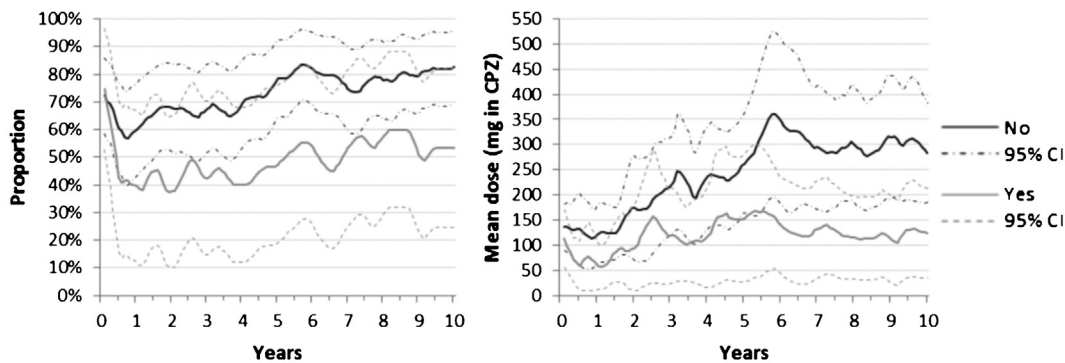[f] Significance from Mann–Whitney's U test.
[g] Significant after Benjamini–Hochberg correction.

Functioning (SOFAS)

Remission

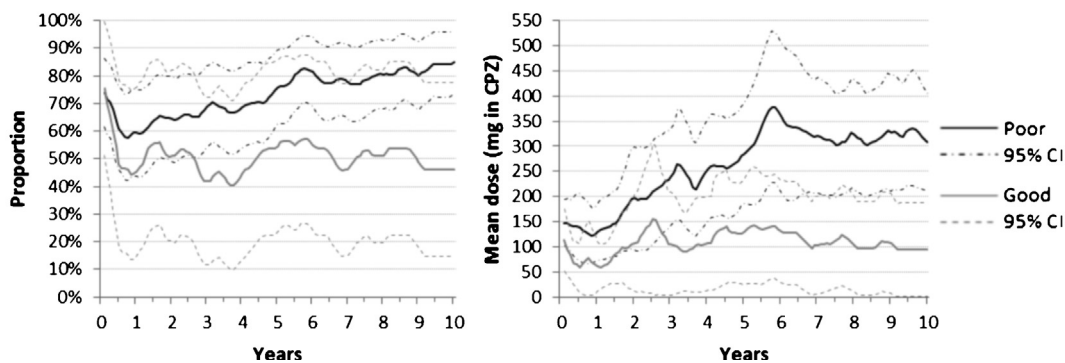## Clinical Global Impression (CGI)

Fig. 3. Mean antipsychotic dose (mg in chlorpromazine equivalents) and proportion (%) of antipsychotic use during ten-year follow-up after onset of illness divided by scores in SOFAS (Social and Occupational Functioning Assessment Scale; relatively good: 60 points or more; impairments: less than 60 points), remission status, and CGI (Clinical Global Impression scale; good: from 1 to 3; poor: from 4 to 7). Lines are smoothed using 5-month moving averages.

significantly associated with SOFAS and CGI, but not with remission ($P = 0.068$).

4. Discussion

4.1. Main results

In total, 42% of the subjects had used antipsychotics less than 50% of the time during the first two years of the follow-up, 32% between two to five years, 26% between five to ten years, and 25% during the whole follow-up. Drug-free periods became rarer during the follow-up, indicating steadier antipsychotic use over time.

In the analyses of medication use and outcome, a low antipsychotic dose was associated with a better outcome in all measures, a low proportion of time on antipsychotics with better

CGI, and no drug-free periods with better SOFAS. APP and higher long-term cumulative antipsychotic use were associated with a poorer outcome in all measures.

4.2. Long-term antipsychotic use

We described the proportion of antipsychotic use for ten years after the onset of illness. This is close to the term compliance (the notifications in the medical records concerning untaken described antipsychotics were taken into account), which has been defined as "the extent to which a person's behavior coincides with the medical advice he/she has received" [39]. Because compliance is not an all-or-nothing phenomenon, the term partial compliance is used [40]. In the review by Llorca [40], rates of partial compliance with antipsychotics increased over time with discharge from an inpatient facility, 50% within one year, and 75% within two years.

Our follow-up was longer, with the proportion of antipsychotic use becoming higher after the first years, and remaining at a higher level after five years of illness, which has not been shown in earlier studies.

4.3. Long-term antipsychotic use and outcomes

Systematic information on long-term use of antipsychotic medication is rare. Harrow et al. [17,41] concluded, in their 20-year follow-up study, that not all schizophrenia subjects need continuous antipsychotic medication for a prolonged period. There are also contrary findings questioning the discontinuation of antipsychotic medication [14] and intermittent treatment [13]. These findings concern the early stage of illness, except for the review by Gilbert et al. [12], which studied the withdrawal of antipsychotics mainly within multi-episode schizophrenia. Our results concerning better social and occupational functioning with steady medication supports the preference for continuous antipsychotic treatment over intermittent. On the other hand, we found a better CGI score among subjects who had used antipsychotics less than half of the time, which suggests inter-individual variations in drug response.

Treatment guidelines, such as the guidelines of the American Psychiatric Association [42], recommend maintenance treatment. However, the lowest dose needed is recommended, and after a symptom-free period (the duration varies between guidelines) the gradual discontinuation of antipsychotics is possible. Our results support these recommendations. Within our sample, a good outcome was observed among those who had a low dose, had no drug-free periods, and used medication less than half of the time. Concerning the latter, it is, however, impossible to say whether those subjects with a good outcome and antipsychotic use less than half of the time fulfill the criteria of guided discontinuation as laid down in the guidelines.

APP could be used in some clinically difficult conditions [22]. This could also explain our results concerning the association between APP and poorer outcomes. More severe illness could also explain the association between higher long-term cumulative antipsychotic use and poorer outcome, as increasing the dose of antipsychotics is one strategy in treating treatment-resistance [43]. This could also be considered from the pharmacogenetic viewpoint, while many subjects do not respond well to antipsychotic treatment [44,45].

4.4. Strengths and limitations

Having a population-based sample offers an opportunity to study naturalistic long-term antipsychotic medication use in schizophrenia. Studies of long-term antipsychotic use in natural settings are rare.

Detailed medication data are a considerable strength. All the available medical records were reviewed, and the data were completed with interviews and register data.

Our epidemiologically sound, population-based sample, consisting mostly of outpatients and some people without psychiatric treatment, may reflect less severe illness than in many clinical settings. To decrease the risk of residual confounding in our naturalistic setting with a long follow-up, the most important confounders related to the duration and severity of illness were taken into account. However, subjects with more severe illness or treatment-resistant schizophrenia may receive higher doses of antipsychotic medication, making higher doses a marker of a more serious illness rather than a cause of decline. Nonetheless, it cannot be ruled out, especially with the cumulative evidence from other studies of potentially harmful effects of years of antipsychotic use on cognition [31],

brain structures, and functioning [32], that the findings reflect a true causal association.

The limitations are that the sample was small and the subjects were in different phases of the illness. We had one follow-up assessment of outcomes, which makes it difficult to interpret associations between medication and outcome as causal. Limitations of the data on medication are: a lack of information on the use of other medication, such as anxiolytics or mood stabilizers; the register data were only available for the year 1997; and we had no information on symptoms or exposure to antipsychotics among non-participants making non-response bias possible.

4.5. Conclusions

Schizophrenia is a heterogeneous condition, and so are responses to antipsychotics. Clinically, it is important to detect these different drug response groups, including those managing with low doses or tolerating pauses or even discontinuation.

In our sample, the use of antipsychotic medication increased during, and was relatively stable after, the first five years of illness. A higher long-term cumulative dose and antipsychotic polypharmacy were associated with a poorer outcome in all measures, reflecting perhaps treatment resistance. A better outcome in all measures was associated with a low dose, better CGI with a proportion of use less than half of the time, and better SOFAS with having no drug-free periods. These findings regarding a better outcome point to heterogeneity of schizophrenia, and also raise questions for future research on how to identify subjects with schizophrenia who benefit from long-term medication, and subjects who manage without doses or with low doses.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eurpsy.2016.03.002.

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