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Discontinuation of antipsychotics in individuals with first-episode schizophrenia and its association to functional outcomes, hospitalization and death: a register-based nationwide follow-up study

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Abstract

Background. Discontinuation of antipsychotic medication may be linked to high risk of relapse, hospitalization and mortality. This study investigated the use and discontinuation of antipsychotics in individuals with first-episode schizophrenia in relation to cohabitation, living with children, employment, hospital admission and death.

Methods. Danish registers were used to establish a nationwide cohort of individuals ⩾18 years with schizophrenia included at the time of diagnosis in1995–2013. Exposure was antipsychotic medication calculated using defined daily dose and redeemed prescriptions year 2–5. Outcomes year 5–6 were analysed using binary logistic, negative binomial and Cox proportional hazard regression.

Results. Among 21 351, 9.3% took antipsychotics continuously year 2–5, 38.6% took no antipsychotics, 3.4% sustained discontinuation and 48.7% discontinued and resumed treatment. At follow-up year 6, living with children or employment was significantly higher in individuals with sustained discontinuation (OR 1.98, 95% CI 1.53–2.56 and OR 2.60, 95% CI 1.91–3.54), non-sustained discontinuation (OR 1.25, 95% CI 1.05–1.48 and 2.04, 95% CI 1.64–2.53) and no antipsychotics (OR 2.00, 95% CI 1.69–2.38 and 5.64, 95% CI 4.56–6.97) compared to continuous users. Individuals with non-sustained discontinuation had more psychiatric hospital admissions (IRR 1.27, 95% CI 1.10–1.47) and longer admissions (IRR 1.68, 95% CI 1.30–2.16) year 5–6 compared to continuous users. Mortality during year 5–6 did not differ between groups.

Conclusion. Most individuals with first-episode schizophrenia discontinued or took no antipsychotics the first years after diagnosis and had better functional outcomes. Non-sustained discontinuers had more, and longer admissions compared to continuous users. However, associations found could be either cause or effect.

Introduction

Individuals with first-episode schizophrenia are internationally recommended maintenance treatment with antipsychotic medication for approximately 2 years [National Institute for Health and Care Excellence (NICE), 2014]. Antipsychotics reduce psychotic symptoms and to some degree prevent relapse; but for some individuals, unwanted side effects such as weight gain, sedation or movement disorders are observed (Leucht et al., 2009). Reviews find that individuals with first-episode psychosis including schizophrenia have a high risk of relapse following discontinuation of antipsychotic medication (Leucht et al., 2012; Thompson et al., 2018; Zipursky, Menezes, & Streiner, 2014), but some individuals have not relapsed despite discontinuing medication in the first years after diagnosis (Gotfredsen et al., 2017; Morgan et al., 2014). When defining goals and recovery, individuals with first-episode psychosis emphasize the importance of not only symptom reduction by medication but also psychosocial aspects of life such as education, work, finances, family and social relationships (Iyer, Mangala,

Anitha, Thara, & Malla, 2011). Hakulinen et al. (2019) found individuals with schizophrenia at high risk of being unemployed and living alone throughout their life. Although, a randomized controlled trial showed better social and vocational function 7 years after dose reduction including discontinuation of antipsychotic medication (Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013).

Discontinuation of antipsychotic medication in individuals with first-episode schizophrenia is described in a few population-based studies and linked to a high risk of hospitalization and mortality (Kroken et al., 2014; Tiihonen, Tanskanen, & Taipale, 2018). However, no population-based follow-up study has described the use and discontinuation of antipsychotic medication in individuals with first-episode schizophrenia in relation to both social and vocational function, hospital admission and mortality. Thus, the following research question was defined: How is the use and discontinuation of antipsychotic medication in individuals with first-episode schizophrenia in relation to subsequent *cohabitation, children, employment, hospitalization, and death*?

Methods

The study was designed as a nationwide follow-up study with data from Danish population-based registries. Every resident in Denmark has a unique civil registration number, the cpr-number, which was used to link information from the registries (Pedersen, 2011). The study was approved by the Danish Data Protection Agency (Jnr P-2020-88). The analyses were conducted on anonymized data and therefore neither patient consent nor ethical approval was required by Danish law.

Individuals were included at time of diagnosis; exposure was use of antipsychotic medication year 2–5; and outcomes were measured from year 5–6.

Study population

Individuals aged ⩾18 years were included when diagnosed with schizophrenia (ICD-10: F20.x) from 1 January 1995 to 1 January 2013. Schizophrenia diagnoses were retrieved from the Danish Psychiatric Central Research Register (Mors, Perto, & Mortensen, 2011) which has proven to have a high validity (Uggerby, Østergaard, Røge, Correll, & Nielsen, 2013). Data on completion of upper secondary school or higher (student and highest education) were retrieved from The Danish Education Register (Jensen & Rasmussen, 2011). In case of emigration, sentence to treatment in forensic psychiatry or death during the first 2 years after diagnosis individuals were excluded.

Exposure to antipsychotic medication

Exposure was redeemed prescriptions of antipsychotic medication in therapeutic dose during year 2–5. The study population was divided into four groups based on the pattern of use of antipsychotic medication (AP) (online Supplementary Fig. S1): AP1) continued exposure; AP2) discontinuation of antipsychotics and sustained either no antipsychotic medication or a dose a dose below therapeutic level; AP3) non-sustained discontinuation of antipsychotic medication defined by discontinuation followed by resumption without limits to number of discontinuation/resumption trials; AP4) no antipsychotic medication. Exposure to antipsychotics in therapeutic dose the first 2 years after diagnosis was assumed and therefore individuals not taking antipsychotics at year 2 were assigned to AP3 if they resumed antipsychotics during the exposure period. In case of emigration, sentence to treatment in forensic psychiatry or death within year 2–5 individuals was excluded.

The Danish National Prescription Registry (Pottegård et al., 2017) provided information on redeemed prescriptions of antipsychotic medication (ATC code of N05Ax except N05AN Lithium). Exposure was calculated by: [(number of tablets × strength)/defined daily dose(DDD)] × 1.15 + 14 days as described by Tiihonen et al. (2011). The calculation of long acting injectables was identical except number of tablets was substituted with units of the injectable antipsychotic. The calculated exposure time had to be minimum 30 days except for long acting injectables. The registry did not record medication during hospitalization or free-of-charge medication offered to patients with recent onset schizophrenia (Jensen, Andersen, Jimenez-Solem, & Lund, 2021). Therefore, data on exposure the first 2 years after diagnosis was discarded.

Functional outcomes, hospitalization and death

Information on living with partner (cohabitation with partner or married), living with children (living with own or partners children under 18 years) and employment (work as primary income source or registered student) was retrieved at year 6. Data on substance or alcohol misuse (ICD-10 diagnosis or misuse treatment in the municipality), psychiatric outpatient clinic contacts and inpatient admissions, involuntary admission, coercion and death during year 5–6 were registered. Data were gathered from Befolkningen register (BEF) (Thygesen, Daasnes, Thaulow, & Brønnum-Hansen, 2011), The Employment Classification Module (AKM) (Petersson, Baadsgaard, & Thygesen, 2011), Danish Register for Evaluation of Marginalization (DREAM) (Hjollund, Larsen, & Andersen, 2007), Danish Education Register (UDDA), Danish National Patient Registry (Schmidt et al., 2015), The National Alcohol Treatment Register, Register of Drug Abusers Undergoing Treatment, The Danish Psychiatric Central Research Register (Mors et al., 2011), The Register of National Coercive Measures in Psychiatric Treatment and Danish Register of Causes of Death (Helweg-Larsen, 2011).

Statistical analysis

Characteristics of the study population and outcomes were described 2 (baseline) and 6 years (follow-up) after diagnosis excluding those sentenced in forensic psychiatry, emigrated or death from year of diagnosis to respectively year 2 and year 6. Binary outcomes at year 6 were analysed using binary logistic regression excluding those sentenced in forensic psychiatry, emigrated or death from year of diagnosis to year 6. Count outcomes between year 5 and 6 were analysed using negative binomial regression because evidence of overdispersion made Poisson regression not relevant. Cox proportional hazard ratios (HR) were estimated for all-cause mortality and death by suicide between year 5 and year 6. Count and time to event outcomes were estimated for those not excluded during year 2–5, and during year 5–6 they were censored at death, emigration and sentence to treatment. AP1 (continuous AP) was predefined as reference group in all analyses comparing groups, since continuous treatment with antipsychotics was assumed to be the standard recommendation.

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Sensitivity analyses of exposure and outcomes were performed to estimate influence of potential confounders and are presented in the online Supplementary material. The grace period of 14 days in calculation of AP groups was prolonged by adding another 60 days (conservative ap status) and thereby allowing for prescriptions to last longer; half DDD was used to reflect individuals with first-episode schizophrenia might take lower dosages (half DDD ap status); individuals admitted to psychiatric hospital were assumed to take antipsychotic medication (admissions ap status) since data on medication during admissions were missing; analyses conducted on half of the study population recently included (latest half ap status) to study potential influence of focus on lower dosages and patient autonomy; adjusting for other F2 diagnoses preceding schizophrenia (other F2 diagnosis preceding schizophrenia ap status). Furthermore, employment data were analysed using a newer and more detailed database (DREAM) to test data quality from AKM. In order to determine potentially increased mortality year 2–5 and its influence on main analyses, sensitivity analyses were conducted with AP exposure handled as a time-varying covariate year 2–5 and death year 2 and 5 as outcome in Cox proportional hazards regression. The p values < 0.05 were regarded significant. Analyses were performed with SPSS version 27 and Stata version 16.

Results

Characteristics of the study population

Inclusion, exclusion and follow-up of the study population are illustrated in Fig. 1. Characteristics of the study population ($N = 23\,268$) 2 years after diagnosis are described for AP1–4 based on exposure year 2–5 in online Supplementary Table S1. Regarding diagnosis, median age at diagnosis was 32.5 years (interquartile range: 24.0–43.8) and 36.5–53.9% had another F2 diagnosis preceding schizophrenia (F2 except F20). Half (49.7%) of individuals in AP1 (continuous AP) were diagnosed as inpatients (diagnosing place) but only one-third (29.7%) in AP4 (no AP). The antipsychotic groups differed significantly on all baseline characteristics except living with a partner.

Use and discontinuation of antipsychotics

One-tenth (9.3%, $n = 1985$) of the study population at year 5 (total $N = 21\,351$) took antipsychotic medication continuously 2–5 years after diagnosis (AP1) and 38.6% ($n = 8251$) took no antipsychotic medication (AP4). Sustained discontinuation (AP2) was registered for 3.4% ($n = 721$) and almost half (48.7%, $n = 10\,394$) of the study population discontinued and resumed treatment with antipsychotic medication (AP3). In sensitivity analyses, four different calculations of AP groups were used (online Supplementary Fig. S2).

Functional outcomes, substance/alcohol misuse and coercion

Social and vocational function for those not excluded at year 6 ($N = 20\,821$) was approached by describing outcomes of living with a partner, living with children and employment. Employment ranged from 4.9% to 22.5%, a third (38.7%) lived with a partner and 12.7% lived with children. Sensitivity analysis using employment data from DREAM did not change this result (online Supplementary Table S2). The majority had no alcohol (93.7%) or substance misuse (91.4%) during year 5–6 (Table 1). Thus, 6 years after diagnosis few individuals were employed, some lived with their partner or children and the majority had no alcohol or substance misuse.

Analyses of living situation, employment, misuse and coercion are illustrated in Fig. 2 and summarized in online Supplementary Table S3. The odds ratio (OR) of living with children and employment at year 6 was significantly higher for individuals in AP2 (sustained discontinuation) (OR 1.98, 95% CI 1.53–2.56 and 2.60, 95% CI 1.91–3.54), AP3 (non-sustained discontinuation) (OR 1.25, 95% CI 1.05–1.48 and 2.04, 95% CI 1.64–2.53) and AP4 (no AP) (OR 2.00, 95% CI 1.69–2.38 and 5.64, 95% CI 4.56–6.97). Having no substance misuse and no involuntary admission during year 5–6 occurred significantly less in individuals in AP2 (sustained discontinuation) (OR 0.66, 95% CI 0.49–0.90 and 0.49, 95% CI 0.33–0.73) and AP3 (non-sustained discontinuation) (OR 0.66, 95% CI 0.54–0.80 and 0.54, 95% CI 0.42–0.71). Individuals in AP4 (no AP) had significantly higher OR of no alcohol misuse (OR 1.40, 95% CI 1.14–1.71) and no coercion (OR 1.26, 95% CI 1.04–1.53). The sensitivity analysis assuming antipsychotics during admission, changed levels of significance and OR, e.g. the OR of no alcohol misuse in AP4 (no AP), almost doubled and became significant (online Supplementary Table S4). In the remaining sensitivity analyses, no confidence intervals around the point estimate crossed 1. Analyses assuming excluded individuals had no employment was performed, but results were similar to main analyses (data not shown). Individuals discontinuing antipsychotics seemingly had overall better functional outcomes, but higher risk of substance misuse, coercion during admission or involuntary admissions to psychiatric hospital.

Hospitalization and death

Contacts to psychiatric outpatient clinic and psychiatric hospital admissions were assumed associated with severity of schizophrenia and relapse. Incidence rate (IR) and incidence rate ratio (IRR) are outlined in Table 2. The number of clinic contacts was significantly lower for individuals in AP2 (sustained discontinuation) (IRR 0.74, 95% CI 0.62–0.88) and AP4 (no AP) (IRR 0.60, 95% CI 0.55–0.67), but higher in AP3 (non-sustained discontinuation) (IRR 1.17, 95% CI 1.06–1.29). The number (IRR 1.27, 95% CI 1.10–1.47) and length (IRR 1.68, 95% CI 1.30–2.16) of admissions were significantly higher for individuals in AP3 (non-sustained discontinuation). Clinic contacts and admissions of non-users (AP4) and the length of admissions in AP2 (sustained discontinuation) decreased in the sensitivity analysis admissions ap status (online Supplementary Table S5). Latest half ap status analysis showed shorter length of admission for AP1–4. Individuals with non-sustained discontinuation (AP3) had more clinic contacts, admissions and time in psychiatric hospital and thus probably more severe symptoms and relapse. Individuals not taking (AP4) or sustaining discontinuation of antipsychotics (AP2) had fewer outpatient clinic contacts. The preponderance did not experience admission to psychiatric hospital during year 5–6 (78.7–89.9%).

Death by all causes ($n = 286$) and death by suicide ($n = 27$) during year 5–6 after diagnosis were analysed with Cox proportional hazard regression providing HR (Table 3) and showed that individuals in AP 2–4 did not have reduced HR of death by all causes or suicide. Sensitivity analyses (online Supplementary Table S6) using conservative ap status and half DDD ap status reached model significance for death by all causes

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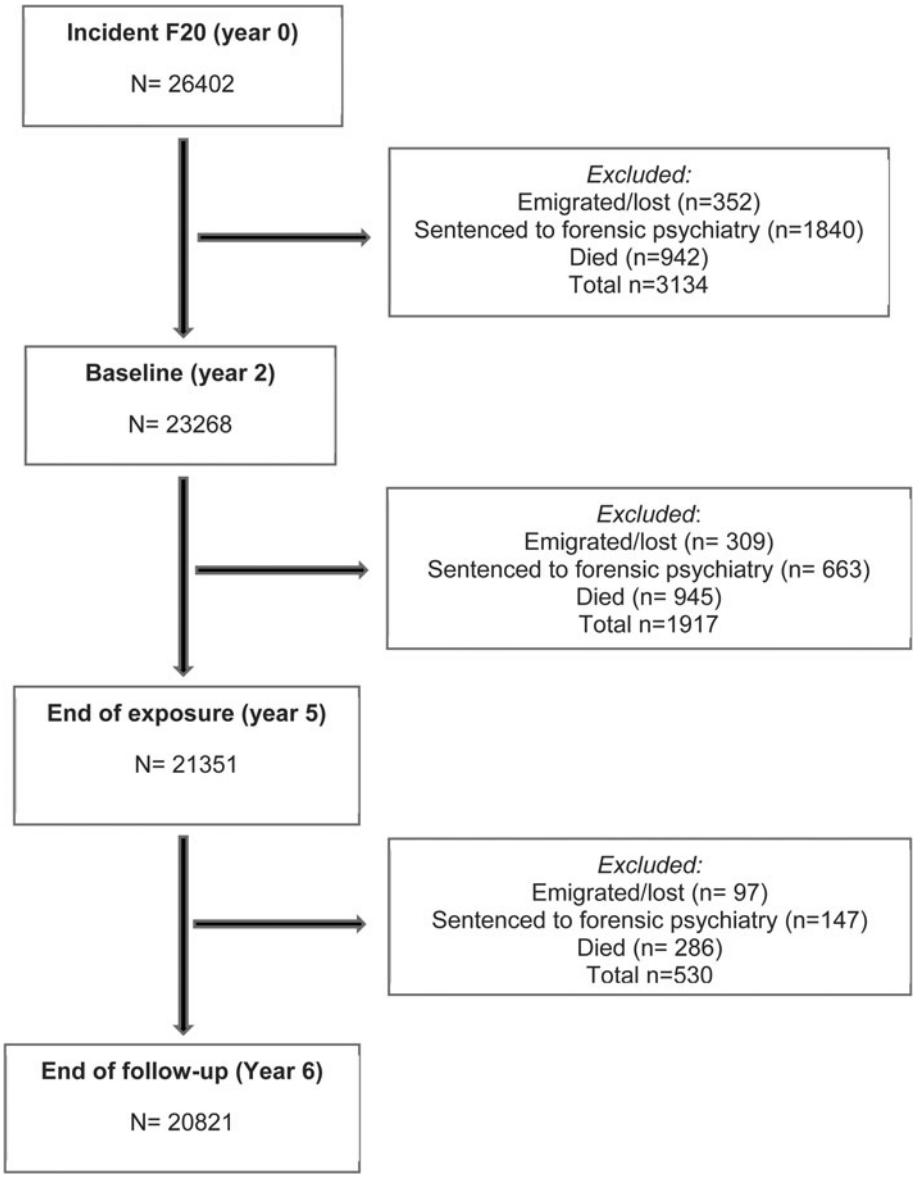

Fig. 1. Flowchart of inclusion and exclusion of study population.

and death by suicide, but no group was significantly different from AP1 (continuous AP). In sensitivity analysis of death during year 2–5 (online Supplementary Table S7), HR of death by all causes ($n = 945$) was significantly higher in individuals in AP4 (no AP) (HR 1.35, 95% CI 1.02–1.52) and death by suicide ($n = 93$) was significantly higher in individuals in AP2 (sustained discontinuation) (HR 5.49, 95% CI 1.83–16.47) and AP3 (non-sustained discontinuation) (HR 4.43, 95% CI 1.83–10.72). There might be a higher risk of death by suicide especially for individuals who stop taking their antipsychotic medication [AP2 (sustained discontinuation) and AP3 (non-sustained discontinuation)] but estimates were imprecise and non-significant in our main analysis.

Discussion

The present study is a register-based nationwide follow-up study including 23.268 individuals with first-episode schizophrenia, their use of antipsychotics 2–5 years after diagnosis and outcomes 5–6 years after diagnosis. Only the minority took antipsychotic medication continuously, two-fifths took no antipsychotics and half discontinued, although most resumed taking antipsychotics. Six years after diagnosis significantly more individuals with sustained discontinuation, non-sustained discontinuation or no antipsychotics lived with children or were employed compared to continuous users. The majority did not experience admission to psychiatric hospital during 5–6 years after diagnosis, but individuals with non-sustained discontinuation of antipsychotics had significantly longer and more psychiatric hospitalizations compared to continuous users. Mortality analyses year 5–6 were non-significant and estimates were imprecise.

Study population

In this study, individuals not taking antipsychotics (AP4) had the lowest percentage of other F2 diagnoses preceding schizophrenia and were less often diagnosed as inpatients, which indicates shorter illness duration and less severe debut. Age of the study population resembles a Norwegian (Kroken et al., 2014) and a Finnish (Tiihonen et al., 2018) cohort of inpatients discharged from hospital with a diagnosis of schizophrenia.

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Table 1. Characteristics of the study population at follow-up

	AP 1 (continuous AP) $n = 1940$	AP 2 (sustained discontinuation) $n = 703$	AP 3 (non-sustained discontinuation) $n = 10\,124$	AP 4 (no AP) $n = 8054$	Total $N = 20\,821$	Lost to follow-up (year 5–6) $N = 530$[d]
Outcomes measured year 6	Count (column%)	Count (column%)	Count (column%)	Count (column%)	Count (column%)	Count (column%)
Sex (female)	856 (44.1)	317 (45.1)	4709 (46.5)	3449 (42.8)	9331 (44.8)	205 (38.7)
Age at diagnosis [median (25–75%)]	34.9 (26.3–45.0)	32.6 (24.1–43.1)	31.2 (23.8–41.8)	31.2 (23.5–43.4)	31.6 (23.8–42.7)	38.5 (26.8–55.6)
Immigrants	186 (9.6)	107 (15.2)	1418 (14.0)	1237 (15.4)	2948 (14.2)	94 (17.7)
Other F2 diagnosis preceding schizophrenia	1041 (53.7)	310 (44.1)	5217 (51.5)	2888 (35.9)	9146 (43.9)	265 (50.0)
Diagnosing place (inpatient)	960 (49.5)	317 (45.1)	4509 (44.5)	2303 (28.6)	8089 (38.9)	232 (43.8)
Index hospitalization length (days) [median (25–75%)]	54 (18–111)	60 (24–134)	61 (25–120)	47 (16–91)	55 (22–112)	43 (12–96)
Education (completed upper secondary school)[a]	765 (41.2)	302 (45.4)	4475 (46.2)	3652 (48.1)	9194 (46.4)	52 (31.7)
Employment (work or study)[b]	95 (4.9)	83 (11.8)	962 (9.5)	1809 (22.5)	2949 (14.2)	19 (4.6)
Living with partner[c]	627 (37.9)	267 (38.2)	3711 (37.0)	3271 (41.0)	7975 (38.7)	73 (41.0)
Living with children[c]	167 (8.7)	111 (15.9)	1068 (10.6)	1281 (16.1)	2627 (12.7)	11 (6.2)
Outcomes measured year 5–6						
No alcohol misuse	1804 (93.0)	662 (94.2)	9406 (92.9)	7642 (94.9)	19 514 (93.7)	457 (86.2)
No substance misuse	1810 (93.3)	634 (90.2)	9127 (90.2)	7467 (92.7)	19 038 (91.4)	443 (83.6)
Psychiatric outpatient clinic contacts [median (25–75%)]	5 (0–13)	0 (0–8)	5 (0–15)	0 (0–4)	2 (0–11)	0 (0–3)
No psychiatric hospital admission	1595 (82.2)	588 (83.6)	7963 (78.7)	7238 (89.9)	17 384 (83.5)	417 (78.7)
Number of psychiatric hospital admissions [median (25–75%)]	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Length of psychiatric hospital admissions (days) [median (25–75%)]	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–3)
No involuntary admissions	1877 (96.8)	658 (93.6)	9536 (94.2)	7746 (96.2)	19 817 (95.2)	474 (89.4)
No coercion	1797 (92.6)	634 (90.2)	8996 (88.9)	7575 (94.1)	19 002 (91.3)	425 (80.2)

[a]4.9% missing.
[b]0.1% missing.
[c]1.0% missing.
[d]Missing in lost to follow-up variables education (69.1% missing), employment (22.3% missing), living with partner (66.4% missing) and living with children (66.4% missing).

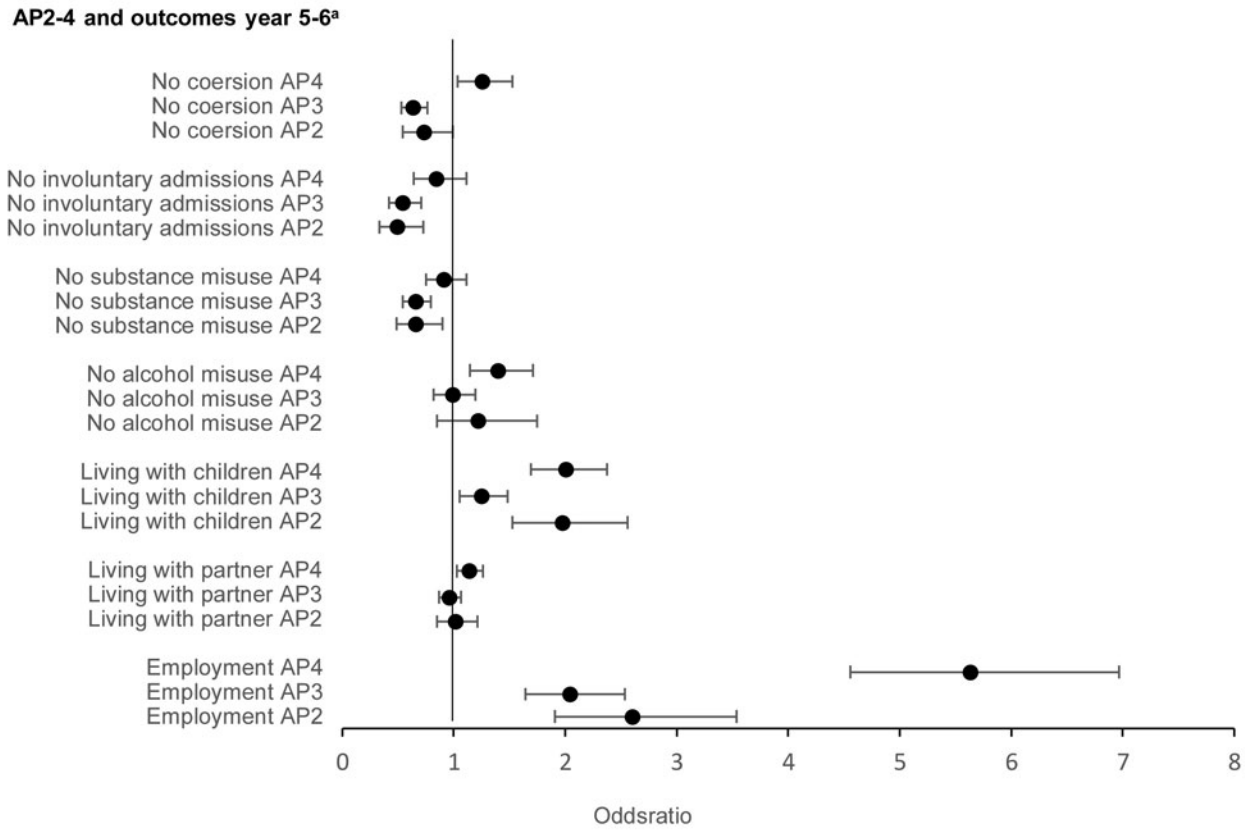

Fig. 2. Forest plot of odds ratios of living situation, employment, alcohol and substance misuse, involuntary admissions and coercion.

Antipsychotic use and discontinuation

In this study, half of individuals with schizophrenia discontinued antipsychotics 2–5 years after diagnosis (AP2 and AP3). Two nationwide register-based studies found high rates of discontinuation. A Finnish study of hospitalized patients with schizophrenia (Tiihonen et al., 2011) found 45.7% took their initial antipsychotic medication more than 30 days and a Swedish study reported 55% of patients with first-episode psychosis had discontinued antipsychotics during the first 5 years after first admission to psychiatric hospital (Strålin & Hetta, 2019). The risk of discontinuation might accumulate as time passes. Five years after diagnosis 58.0% took antipsychotic medication (AP1 and AP3), which is comparable to the 66% (46 patients) found by Harrow, Jobe, and Faull (2012) at 4.5 years follow-up. Five years after diagnosis 42.0% of individuals in this cohort took no antipsychotics (AP2 and AP4) which is a little higher than 34% found by Gotfredsen et al. (2017) 5 years after initial treatment for a first-episode psychosis (primarily schizophrenia).

Functional outcomes

The OR of living with children or employment was significantly higher for individuals who discontinued (AP2 and AP3) or took no antipsychotics compared to continuous users (AP1), which might indicate a subgroup managing without antipsychotic medication. A clinical study by Wils et al. (2017) found an association of higher function (GAF) and labour market affiliation with no antipsychotic medication and remission of psychotic symptoms 10 years after initial treatment for first-episode psychosis (primarily schizophrenia). Furthermore, Wunderink et al. (2013) found higher functional remission 7 years after a randomized intervention of dose-reduction compared to maintenance treatment in first-episode psychosis. However, the follow-up was done 5 years after end of intervention and treatment was uncontrolled during the 5 years, hence interpretation was difficult.

Alcohol and substance misuse, hospitalization, involuntary admissions and coercion

Individuals discontinuing antipsychotics (AP2 and AP3) had significantly more substance misuse. Similarly, Kroken et al. (2014) found an increased risk of antipsychotic discontinuation in patients with schizophrenia having a comorbid alcohol/drug problem. Although, when taking no antipsychotics (AP4) this study found significantly less alcohol misuse and coercion 5–6 years after diagnosis. Discontinuers (AP2 and AP3) experienced significantly more involuntary admissions and coercion like Kroken et al. found involuntary inpatient treatment increased the risk of antipsychotic discontinuation.

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Table 2. Incidence rate and incidence rate ratio of psychiatric outpatient clinic contacts, hospital admissions and length of stay

Outcomes measured year 5–6 total $N = 21\,348$		AP 1 (continuous AP)[a] $n = 1985$			AP 2 (sustained discontinuation) $n = 721$			AP 3 (non-sustained discontinuation) $n = 10\,392$			AP 4 (no AP) $n = 8250$		
		IR/IRR	95% CI	*p* value model	IR/IRR	95% CI	*p* value	IR/IRR	95% CI	*p* value	IR/IRR	95% CI	*p* value
Outpatient clinic contacts	IR	9.40	8.59–10.29	<0.01	6.96	5.99–8.10		10.95	10.53–11.40		5.68	5.43–5.94	
	IRR				0.74	0.62–0.88	<0.01	1.17	1.06–1.29	<0.01	0.60	0.55–0.67	<0.01
Number of admissions	IR	0.38	0.33–0.43	<0.01	0.33	0.26–0.41		0.48	0.46–0.51		0.20	0.18–0.21	
	IRR				0.86	0.66–1.11	0.25	1.27	1.10–1.47	<0.01	0.52	0.44–0.60	<0.01
Length of admissions (days)	IR	8.99	7.13–11.32	<0.01	12.41	8.46–18.21		15.06	13.62–16.66		8.12	7.25–9.10	
	IRR				1.38	0.88–2.16	0.16	1.68	1.30–2.16	<0.01	0.90	0.70–1.17	0.44

IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval.
[a]Reference group.

During the follow-up period, the majority (83.5%) had no psychiatric hospitalizations. Compared to continuous users (AP1), individuals with sustained discontinuation (AP2) or no antipsychotics (AP4) had fewer admissions. In contrast, Tiihonen et al. (2011, 2018) found patients with a first hospitalization for schizophrenia with continuous use of antipsychotics had an associated lower risk for rehospitalization compared to discontinuation, but they did not report resumption of antipsychotics after discontinuation. The contrasting results might therefore partly be explained by intermittent use of antipsychotics, and in this study individuals with non-sustained discontinuation (AP3) had more and longer hospitalizations compared to continuous users. Thus, discontinuation of antipsychotics might increase the risk of experiencing relapse, but some patients discontinue antipsychotics the first years after diagnosis without relapsing.

Death including suicide

Individuals discontinuing (AP2 and AP3) or not taking antipsychotics (AP4) did not have reduced risk of death including death by suicide during 5–6 years after diagnosis when compared to continuous users (AP1). This finding corroborates with a previous review of randomized controlled trials (Schneider-Thoma et al., 2018), which found no increased mortality risk in patients with schizophrenia taking antipsychotics compared to placebo, but the majority of trials were short. Furthermore, a Swedish nationwide register study found recent dispensions of antipsychotics did not influence risk of death among individuals with first-episode psychosis (Strålin & Hetta, 2019). On the contrary, excess mortality in individuals with schizophrenia not taking antipsychotics has been reported in register-based nationwide studies comparing users with non-users (Tiihonen et al., 2018; Torniainen et al., 2015) and in studies using within-individual comparisons (Strømme et al., 2021; Taipale et al., 2020). A few observational studies have reported antipsychotic use associated with lower risk of suicide (Strømme et al., 2021; Tiihonen, Mittendorfer-Rutz, Torniainen, Alexanderson, & Tanskanen, 2016) among individuals with schizophrenia. Online Supplementary analyses in this study showed a significantly increased risk of suicide during year 2–5 after discontinuing antipsychotics (AP2 and AP3).

Strengths and limitations

This is the largest register-based study of individuals with first-episode schizophrenia describing both use, discontinuation and resumption of antipsychotic medication and allowing for switch of antipsychotics. Furthermore, it is the first cohort study including individuals with schizophrenia at time of diagnosis regardless of being inpatient/outpatient and linking antipsychotic use and discontinuation with both functional outcomes, hospitalization and death. Danish registers used in the study have nationwide coverage and include every resident in Denmark, which limits risk of selection bias.

A limitation of the study was risk of misclassification and an underestimation of antipsychotic use due to missing data on medication during admissions and free-of charge antipsychotic medication. Medication adherence the first years after a schizophrenia diagnosis is difficult (Le Quach et al., 2009) and this study has no information on whether patients took their medication potentially leading to unmeasured confounding and overestimating antipsychotic use. Furthermore, the method used to define exposure although previously used (Tiihonen et al., 2011) has

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Table 3. Hazard ratio of death by all causes and death by suicide during year 5–6

Outcomes measured year 5–6	AP 1 (continuous AP)[a]	AP 2 (sustained discontinuation)			AP 3 (non-sustained discontinuation)			AP 4 (no AP)			Total
	Reference group	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	*p* value model
Death by all causes		0.57	0.25–1.28	0.17	0.76	0.52–1.11	0.15	0.76	0.52–1.12	0.17	0.41
Death by suicide		1.40	0.13–15.48	0.782	1.88	0.44–8.09	0.39	0.51	0.12–3.12	0.55	0.10

HR, hazard ratio; CI, confidence interval.
[a]Reference group.

uncertainties. DDD used in calculations describes higher doses than the minimum effective dose (Leucht et al., 2014). Sensitivity analysis attempted to account for potential use of lower dosages and missing data on medication. Variations over time were reduced by completeness and consistency of the registries and by making sensitivity analyses. Continuous users were predefined as reference group but was small, which lead to imprecise estimates. Excluding individuals due to sentence to treatment in forensic psychiatry or death potentially introduced selection bias as it can be hypothesized that these were more severely ill. Mortality analyses were imprecise due to small number of events. Proxies for function and relapse are assumptions and therefore must be interpreted with caution. Results are interpreted as descriptive and not as causal effects as the design of the study did not account for potentially reverse causation or confounding by indication as indicated by group differences already before exposure. The indication of discontinuing antipsychotics is remission of psychotic symptoms which is associated with functional remission (Schennach-Wolff et al., 2009). In contrast, the effect of healthy adherer and sick stopper must also be kept in mind.

Conclusion

The results suggest most individuals with first-episode schizophrenia discontinue antipsychotic medication during the first years after diagnosis or do not take antipsychotics in therapeutic doses. Six years after diagnosis discontinuers and non-users had overall better functional outcomes regarding living with children and employment compared to individuals taking antipsychotics continuously. Individuals sustaining discontinuation or not taking antipsychotics had fewer outpatient clinic contacts 5–6 years after diagnosis, but those who resumed treatment with antipsychotics had more clinic contacts and admissions to psychiatric hospital. Individuals discontinuing antipsychotics experienced more substance misuse, coercion and involuntary admissions 5–6 years after diagnosis. No differences were found in mortality risk 5–6 years after diagnosis, but estimates were imprecise. The associations found between antipsychotic use and outcomes could be either cause or effect. Clinical implications are awareness of frequent discontinuation of antipsychotics in recent onset schizophrenia. Several reported outcomes are useful in shared decision making and in development of treatment guidelines. The study might indicate two subgroups of discontinuers; one subgroup with better function and no relapses and another subgroup with severe relapses and substance misuse. Future research should explore antipsychotic use patterns in relation to relapse, function and other patient-oriented goals.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291722002021

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