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Characteristics and predictors of off-label use of antipsychotics in general population sample

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Abstract

Objective: Increasing number of people have been prescribed antipsychotics (APs) off-label in recent decades. This study aimed to identify the characteristics and predictors of receiving prescription of antipsychotics off-label.

Methods: The study sample was part of the Northern Finland Birth Cohort 1966 ($n = 7071$). Data included questionnaires and national register data. Information on prescribed medications was extracted from the national register. The sample was divided into three groups: Persons who had been prescribed APs off-label ($n = 137$), individuals with non-psychotic mental disorders without APs off label ($n = 1478$) and individuals who had been diagnosed with psychosis or bipolar disorder and who had been prescribed APs ($n = 151$). We compared sociodemographic, lifestyle and clinical characteristics between the off-label and the comparison groups using logistic regression.

Results: The most common diagnoses in the off-label group were depression ($n = 96$, 70.1%) and anxiety ($n = 55$, 40.1%). Compared with individuals with non-psychotic mental disorders who were not prescribed APs off-label, individuals with prescribed off-label APs had a lower level of education, lower socioeconomic status, were less often married, had a higher level of somatic and psychiatric morbidity, were more often smokers and more often had a substance abuse disorder and heavy alcohol consumption. When comparing the off-label group to individuals with psychosis or bipolar disorder who used APs, there were less differences, though individuals with psychosis or bipolar disorder had more markers of morbidity and a lower level of education.

Conclusion: Individuals who had been prescribed APs off label had a higher level of mental and somatic morbidity and poorer socioeconomic status than individuals with non-psychotic mental disorders who did not use APs.

KEYWORDS

antipsychotic agent, comorbidity, mental disorders, off-label use, socioeconomic status

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1 | INTRODUCTION

Treatment of schizophrenia, bipolar disorder, and adjunctive medication for a major depressive episode are the most common official indications of antipsychotics (AP).[1] Official on-label indications vary between countries. Off-label use refers to the use of medicine for an unapproved indication. It can also refer to using medicine with a dose outside the approved dosage or use in a patient group that differs from official indications.[2,3]

The number of individuals using APs has rapidly increased globally since the beginning of the 21st century,[4] particularly the off-label use of second-generation APs (SGAPs).[4,5] AP use increased almost 7-fold in 8 years in a study conducted in the United States and increased 10-fold in a study conducted in Norway.[6–8] Hálfdánarson et al studied international trends in AP use from 2005 to 2014 in 16 countries. They found that AP use increased by two-thirds in the study populations.[4] The growth in SGAP use is primarily attributable to increased AP off-label use.[9] A Canadian study examined the prescribing trends of physicians for 5 years and found that 44% of AP prescriptions were classified as off-label prescriptions.[10] AP off-label use has reached as high as 61% of all AP use in the adult population.[9] The most common off-label diagnoses linked to AP off-label prescriptions are anxiety disorders, sleep disorders, mood disorders, post-traumatic stress disorder (PTSD) and mild depression.[9]

The comprehensive systematic review by Maglione et al showed that atypical APs are effective in the treatment of symptoms of anxiety disorders such as generalised anxiety disorder (GAD), obsessive–compulsive disorder (OCD), and PTSD, as well as some personality disorders.[11] Their effectiveness in the treatment of non-psychotic unipolar depression has also been shown, and in many countries such use is considered on-label.[12] Studies of the efficacy of APs in off-label indications are based on clinical trials, which have had relatively short study periods, so the long-term effects are still unknown. Only a few studies have been conducted on APs as a treatment for insomnia[11] and specifically only one small randomised clinical trial[13] and one open label trial[14] on AP medication in primary insomnia, although prescribing low-dose quetiapine for insomnia is a global practice. In 2012, Canadian GPs prescribed 10 times more often low-dose quetiapine for sleeping disorders compared with 2005.[15]

APs cause adverse effects in both on-label and off-label use. However, the adverse effects of off-label use have rarely been studied.[16] Regardless of indication, weight gain, adverse metabolic effects, arterial hypertension, and daytime fatigue are commonly reported side effects of APs.[17] Compared with the number of studies on AP on-label use and the large and increasing number of individuals using APs off-label, the predictors and outcomes of AP off-label use require further study.[11]

Based on previous literature (Table S1), persons using APs off-label are generally aged between 30 and 60 years and women use APs off-label more than men. Off-label use is associated with lower employment, overweight and more unfavourable lifestyle habits such as smoking. In addition, PTSD, OCD, GAD, and somatic morbidity are often associated with AP off-label use. In previous studies, quetiapine has been the most often used AP (Table S1).

Previous studies have not studied background variables such as socioeconomic status and educational level as predicting factors of AP off-label use in a general population. In addition, previous studies have been mainly register based and cross sectional or included a period of a few years (Table S1). AP off-label use has not previously

Significant Outcomes

- Individuals who had been prescribed antipsychotics (APs) off-label had more markers of poor health, had poorer socioeconomic status, consumed more alcohol and smoked more often compared with individuals with non-psychotic mental disorders without APs off-label.
- There were less significant differences between individuals with APs off-label compared with individuals with psychosis or bipolar disorder who used APs, though individuals who had been prescribed AP off-label had a lower morbidity and a higher level of education and sociodemographic background.
- This is one of few studies to analyse the characteristics of antipsychotics off-label use on a subject level, in a prospectively collected general population sample with a long period of follow-up.

Limitations

- The sample size in the off-label group was relatively small.
- The causality between background variables and antipsychotic off-label use is not known.
- The dose, duration or purpose of the medication was not included in the data.

been studied so thoroughly in the prospectively collected general population data.

Analysing factors associating to APs off-label use, in other words factors associating to getting prescription of off-label APs, is important. The results may inform about the validity of prescribing practices—whether it is the clinical severity or some other factors that characterise the group using APs off-label. Knowledge on factors associating to the use may help to understand the increased amount of AP off-label use in general. Eventually, studies analysing factors associating to APs off-label use may help changing the clinical practices and guidelines if needed.

1.1 | Aims of the study

Our aim was to analyse the characteristics and predictors of receiving prescription of antipsychotics off-label in an adult general population sample during period of 14 years, comparing sociodemographic, alcohol consumption, smoking, and clinical characteristics between persons with APs off label and other groups.

2 | MATERIAL AND METHODS

2.1 | Sample

The study sample is part of The Northern Finland Birth Cohort 1966 (NFBC1966). NFBC1966 includes almost all (96%) babies born alive in Oulu and the provinces of Lapland, whose expected date of birth was in 1966 (N = 12,058). The data have been collected from the foetal period to adulthood using various questionnaires, clinical examinations, and national registers.[18] Large data collections using questionnaires and clinical examinations for all the cohort members were conducted in 1997 (31-year study) and 2012 (46-year study).[19,20] During the 46-year study, cohort members were asked to provide their informed consent to combine their data with various national registers (including permission to use register data from the Social Insurance Institution (SII). Before the 46-year study, 10,331 cohort members were still alive and living at known addresses. All cohort members were invited to participate in the 46-year study. The study sample (N = 7071) included those NFBC1966 members who participated in the 46-year study (from 2012 to 2014) and gave their consent to use their data and combine it with national register data. The study was approved by the Northern Ostrobothnia Hospital District Ethical Committee.

2.2 | Data on diagnoses of the sample

Data on psychiatric diagnoses of the sample was obtained from the nationwide Care Register for Health Care (CRHC) register, including all general and psychiatric hospitalisations since the beginning of the cohort study, specialised outpatient treatment since 1998 and primary care outpatient treatment since 2011. The data were supplemented with data from the registers of the Social Insurance Institution of Finland (SII) about the right (i.e., specific diagnoses) to receive reimbursable medication for a psychosis since 1974 and diagnoses providing the right to receive a disability pension and sick leave, as well as data about disability pensions from the Finnish Centre for Pensions (since the early 1970s).

We also used questionnaire data from the 31- and 46-year studies, including questions about lifetime diagnoses of psychosis, depression and other mental health disorders diagnosed by a physician.

Three different diagnostic systems were used during the cohort data collection: ICD-8 (1968–1986), ICD-9 (1987–1995), and ICD-10 (since 1996). The diagnoses included in this study are described in Table S2.

For this study, we only included psychiatric diagnoses from 1 January 1985 (i.e., the year when all cohort members were at least 18 years of age) until the day cohort members started participating in the 46-year study.

2.3 | Data on medication prescriptions and purchases and period of follow-up

All the medication data were collected from SII's national register from 1 January 1998 to the date when the 46-year study started, leading to the follow-up period of this study. SII maintains a register of all prescription medication purchased in Finland. From SII's data, we selected all cohort members who had purchased APs at least once between 1998 and the start of the 46-year study. Psychiatric medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system.[21] In this study, the group of antipsychotics included ATC group N05A (antipsychotics), excluding N05AN (lithium) and N05AB04 (prochlorperazine). Lithium was excluded since it is not used as an antipsychotic and prochlorperazine was excluded since it has been used on-label in Finland for nausea.

2.4 | The definition of antipsychotic off-label use and comparison groups

The sample comprised a total of 7071 cohort members and was divided into three groups: persons who had been

prescribed and who purchased APs off-label ('Off-label group') and two comparison groups. The off-label group ($n = 137$) includes cohort members who purchased at least one prescription of AP medication during the follow-up, had not been diagnosed as having a psychosis or bipolar disorder in any register and had not stated in the 31 or 46-year study questionnaires that they had been diagnosed with a psychosis. The first comparison group ('Comparison group 1'; $n = 1478$) included all subjects who had been diagnosed with a mental health disorder, excluding psychosis and bipolar disorder, and who did not purchase any AP medication during the follow-up. The second comparison group ('Comparison group 2'; $n = 151$) included subjects diagnosed with psychosis or bipolar disorder who had been prescribed and who purchased AP medication during the follow-up. The diagnoses of each group are presented in Table S2.

A total of 5305 cohort members were excluded from the study. A total of 5158 cohort members who had not been diagnosed with a mental disorder and who did not use AP were excluded. Nine cohort members were diagnosed with psychosis or bipolar disorder after the 46-year study and 15 cohort members had only purchased prochlorperazine. A total of 98 cohort members were excluded from the comparison group 1: 29 of them were diagnosed with psychosis or bipolar disorder after the 46-year study, 10 had only purchased prochlorperazine and two had unclear diagnoses (delirium and single episode organic mania). Sixty-nine cohort members diagnosed with psychosis or bipolar disorder were excluded because they received no AP medication during the follow-up.

2.5 | Variables on sociodemographic, lifestyle and clinical characteristics

Several variables describing sociodemographic background, lifestyle and clinical characteristics were collected from national registers, and from questionnaires cohort members made as a part of the 31-year study (Table 1). The socioeconomic status was divided into two subgroups: higher and lower. The higher group included entrepreneurs, upper officials, and lower officials, and the lower group consisted of employees, farmers, students, pensioners, others (unemployed), and unknows. Information for socioeconomic status was missing for 14 individuals, and all the 14 belonged in the comparison group.

2.6 | Statistical analyses

Sociodemographic, lifestyle, and clinical characteristics are presented for the off-label and comparison groups using cross tabulations (categorical variables) or means with standard deviation (SD; age of illness onset) and compared these between all three groups using Chi-square test of analysis of variance, respectively. Number of years with a purchase was compared between all three groups using Chi-square test. The characteristics were also compared between the off-label group and both comparison groups separately using logistic regression. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs) and p values. p Values <0.05 were considered to be statistically significant. All tests were two-tailed. The statistical analyses were conducted using IBM SPSS Statistics, version 27.

3 | RESULTS

3.1 | Characteristics of the off-label group

The study population was divided into three groups: the off-label group and two comparison groups (Figure 1). A total of 65 (47%) of AP off-label group were male and 72 (53%) were female (Table 2). The median onset age for the first psychiatric diagnosis was 39 years (IQR: 35.3–41.0). A total of 96 persons in the AP off-label group (70%) were diagnosed with depression, 55 (40%) with anxiety, 37 (27%) had some form of alcohol disorder and 39 (29%) had a substance abuse disorder. A total of 20 (15%) members in the off-label group had no psychiatric diagnosis (Table 3). The most frequently purchased APs were quetiapine, perphenazine, risperidone and levomepromazine (Table 4).

Regarding the duration of APs off-label use, 72 (53%) individuals had off-label AP purchases only in 1 year, 35 (26%) in two or three separate years, and 30 (22%) in more than three separate years. In the comparison group 2, only 20 (13%) individuals had AP purchases only in 1 year, 27 (18%) in 2 or 3 years, and 104 (69%) in more than 3 years ($p < 0.001$ for the difference between the groups).

3.2 | Comparison of sociodemographic, lifestyle and clinical variables between the off-label group and comparison group 1

Compared with comparison group 1 (i.e., non-psychotic mental illness, no AP purchases), the proportion of females in the off-label group was lower [OR 0.53 (95% CI 0.37–0.75)]. Members of the off-label group were less educated [$OR_{secondary}$ 0.46 (0.29–0.72) and $OR_{tertiary}$ 0.40 (0.29–0.69)], were less often in higher socioeconomic

TABLE 1 Description of variables on sociodemographic, lifestyle and clinical characteristics

Variable	Data source
Educational level (basic level, length of education 9 years/secondary level, length of education 11–12 years/tertiary level, length of education 14-years, equivalent to lower university degrees.)	Statistics Finland's national register (from the year 1997)
Socioeconomic status (high/low)	Statistics Finland's national register (from the year 2000)
Marital status (married or registered relationship/never married/ divorced or widowed)	Digital and Population Data Services Agency register (from the year 1997)
Smoking (non-smoker/former or occasional smoker/current smoker)	The 31-year questionnaire
Alcohol consumption (Abstainer 0 mg/day)/moderate (males <30 mg/ day and females <20 mg/day)/Heavy (males >30 mg/day and females >20 mg/day)[18]	The 31-year questionnaire
Age of illness onset (separate variable for any psychiatric disorder and any psychosis)	The Care register for Health Care, the Finnish outpatient registers, Social Insurance Institution registers, and the Finnish Centre for Pensions registers
Psychiatric diagnoses (Table S2)	The Care register for Health Care and other registers
Psychiatric comorbidities	The Care register for Health Care, Social Insurance Institution registers, and the Finnish Centre for Pensions registers
Somatic illnesses (Table S2)	The Care Register for Health Care
Developmental disorder (Table S2)	The Care Register for Health Care
Family history of mental disorder (separate variables for any parental psychiatric disorder and any parental psychosis)	The Care Register for Health Care

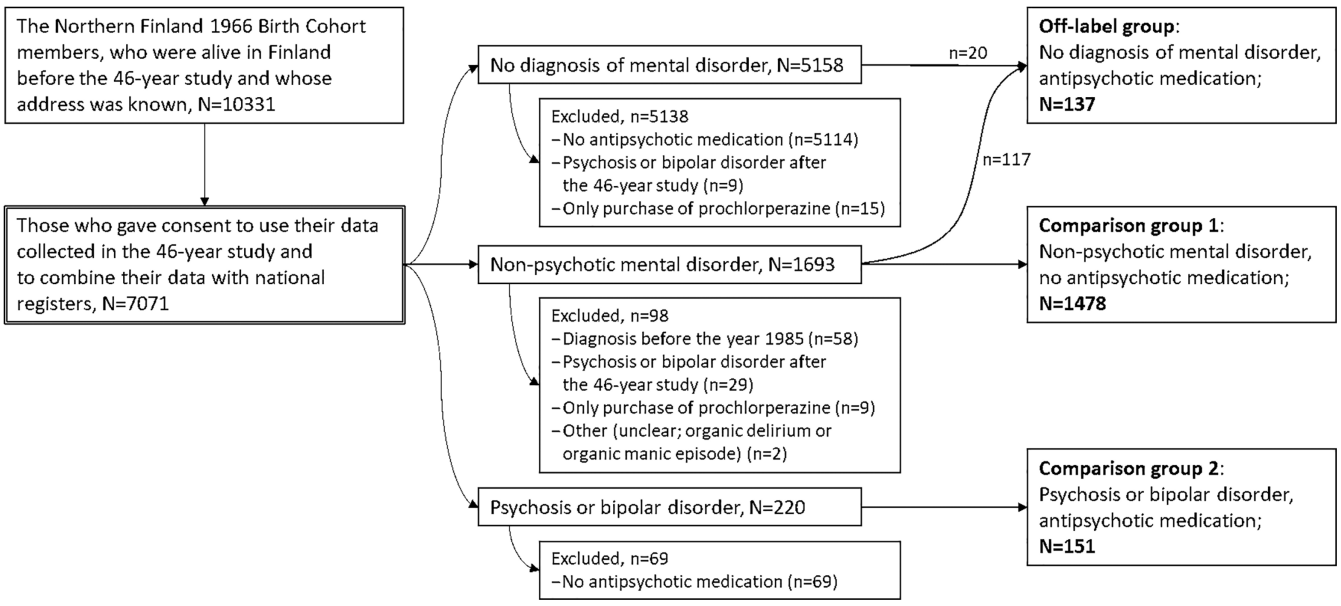

FIGURE 1 The study sample

status [OR 0.55 (0.39–0.79)] and were more likely to be unmarried [1.70 (1.17–2.49)] or divorced/widowed [OR 2.05 (1.13–3.72)] than members of comparison group 1. Members of the off-label group were more likely to be current smokers [OR 1.74 (1.11–2.71)] and consumed more alcohol than members of comparison group 1 [$OR_{heavy/binge}$ 2.22 (1.28–3.85); Table 2].

Members of the off-label group were more often diagnosed with non-psychotic depression than members of comparison group 1 [OR 1.78 (1.22–2.60)]. The off-label

TABLE 2 Sociodemographic background factors and tobacco and alcohol use in antipsychotic off-label use group and comparison groups

Characteristic	Off-label group ($n = 137$) *N* (%)	Comparison 1: Non-psychotic mental illness, no APs ($n = 1478$) *N* (%)	Comparison 2: Psychosis or bipolar disorder, with prescription and purchase of APs ($n = 151$) *N* (%)	*p*-Value	Off-label group vs. Comparison 1 OR (95% CI)	Off-label group vs. Comparison 2 OR (95% CI)
Gender				**<0.001**		
Male	65 (47)	475 (32)	75 (50)		Ref.	Ref.
Female	72 (53)	1003 (68)	76 (50)		0.53 (0.37–0.75)	1.09 (0.69–1.74)
Educational level in 1997				**<0.001**		
Basic	29 (22)	156 (11)	22 (15)		Ref.	Ref.
Secondary	78 (58)	921 (63)	109 (73)		0.46 (0.29–0.72)	0.54 (0.29–1.02)
Tertiary	28 (21)	381 (26)	19 (13)		0.40 (0.29–0.69)	1.12 (0.50–2.50)
Missing	*2 (2)*	*20 (1)*	*1 (1)*			
Socioeconomic status in 2000						
Lower	83 (61)	672 (46)	114 (76)	**<0.001**	Ref.	Ref.
Higher	54 (40)	792 (54)	37 (25)		0.55 (0.39–0.79)	2.01 (1.21–3.32)
Marital status in 1997				**<0.001**		
Married or registered partnership	50 (37)	743 (50)	43 (29)		Ref.	Ref.
Never married	71 (52)	619 (42)	95 (63)		1.70 (1.17–2.49)	0.64 (0.38–1.07)
Divorced or widowed	16 (12)	116 (8)	13 (9)		2.05 (1.13–3.72)	1.06 (0.46–2.45)
Smoking at 31 years				**0.002**		
Non-smoker	39 (35)	552 (43)	41 (32)		Ref.	Ref.
Former/occasional smoker	27 (24)	366 (28)	31 (24)		1.04 (0.63–1.74)	0.92 (0.47–1.80)
Current smoker	46 (41)	375 (29)	55 (43)		1.74 (1.11–2.71)	0.88 (0.49–1.59)
Missing	*25 (18)*	*185 (13)*	*24 (16)*			
Alcohol consuming at 31 years				**<0.001**		
Moderate	79 (70)	1063 (82)	85 (67)		Ref.	Ref.
Abstainer	16 (14)	122 (9)	20 (16)		1.77 (1.00–3.12)	0.86 (0.42–1.78)
Heavy	18 (16)	109 (8)	22 (17)		2.22 (1.28–3.85)	0.88 (0.44–1.76)
Missing	*24 (18)*	*184 (12)*	*24 (16)*			

Note: Statistically significant ($p < 0.05$) *p*-values are in bold. OR = Odds ratio. 95% Cl = 95% confidence interval.

group had more diagnoses of PTSD [OR 2.91 (1.07–7.92)], borderline personality disorder [OR 15.86 (4.97–50.68)], an alcohol disorder [OR 3.20 (2.12–4.84), a substance abuse disorder (OR 3.30 [2.20–4.95)] and other non-psychotic mental disorders (OR 3.01 [1.83–4.93]) compared with comparison group 1. The occurrence of depression and anxiety and stress-related disorders [OR 2.27 (1.56–3.32)], depression and substance abuse disorders [OR 5.18 (3.27–8.20)], anxiety and substance abuse disorders [OR 5.01 (2.71–9.25)] and depression, anxiety, and substance abuse [OR 8.14 (4.12–16.09)] were more common in the off-label group than in comparison group 1. Regarding somatic illnesses, diseases of the nervous system [OR 1.51 (1.05–2.17)] and epilepsy [OR 3.95 (1.94–8.01)] were more common in the off-label group than in comparison group 1, but there was no difference in the rate of diabetes (Table 3).

3.3 | Comparison of sociodemographic, lifestyle and clinical variables between the off-label group and comparison group 2

The gender distribution in comparison group 2 (i.e., psychosis or bipolar disorder and the use of AP) was similar to the off-label group. The off-label group members were

TABLE 3 Illness related factors in antipsychotic off-label use group and comparison groups

Characteristic	Off-label group ($n = 137$) *N* (%)	Comparison 1: Non-psychotic mental illness, no APs ($n = 1478$) *N* (%)	Comparison 2: Psychosis or bipolar disorder, with prescription and purchase of APs ($n = 151$) *N* (%)	*p*-Value	Off-label group vs. Comparison 1 OR (95% CI)	Off-label group vs. Comparison 2 OR (95% CI)
Only self-reported diagnosis*	14 (10)	291 (20)	6 (4)	**<0.001**		
Age of illness onset						
Any psychiatric disorder, mean (SD)	36.7 (8.3)	38.7 (6.9)	31.9 (7.9)	<0.001	0.97 (0.94–0.99)	1.09 (1.05–1.13)
Any psychosis or bipolar disorder**, mean (SD)	N.A.	N.A.	35.3 (7.3)			
Psychiatric diagnosis						
Non-psychotic depression (incl. self-reported)	96 (70)	840 (57)	127 (84)	**<0.001**	1.78 (1.22–2.60)	0.44 (0.25–0.78)
Anxiety and stress related disorders	55 (40)	698 (47)	63 (42)	0.143	0.75 (0.53–1.07)	0.94 (0.59–1.5)
Post-traumatic stress disorder	5 (4)	19 (1)	4 (3)	0.055	2.91 (1.07–7.92)	1.39 (0.37–5.30)
Insomnia	9 (7)	83 (6)	8 (5)	0.913	1.18 (0.58–2.41)	1.26 (0.47–3.36)
Borderline personality disorder	7 (5)	5 (0)	20 (13)	**<0.001**	15.86 (4.97–50.68)	0.35 (0.14–0.86)
Any alcohol disorder (incl. self-reported)	37 (27)	153 (10)	56 (37)	**<0.001**	3.20 (2.12–4.84)	0.63 (0.38–1.04)
Any substance abuse disorder (incl. self-reported)	39 (29)	159 (11)	60 (40)	**<0.001**	3.30 (2.20–4.95)	0.60 (0.37–0.99)
Schizophrenia spectrum disorders	-	-	66 (44)		-	-
Bipolar disorder	-	-	46 (31)		-	-
Other psychosis	-	-	104 (69)		-	-
Other mental disorder	23 (17)	93 (6)	61 (40)	**<0.001**	3.01 (1.83–4.93)	0.30 (0.17–0.52)
No psychiatric diagnosis	20 (15)	-	-			
At least 2 different disorders						
Depression (incl. self-reported) and anxiety and stress related disorders	46 (34)	269 (18)	61 (40)	**<0.001**	2.27 (1.56–3.32)	0.75 (0.46–1.21)
Depression and substance abuse disorder (incl. self-reported)	31 (23)	79 (5)	53 (35)	**<0.001**	5.18 (3.27–8.20)	0.54 (0.32–0.91)
Anxiety and substance use (incl. self-report)	16 (12)	38 (3)	30 (20)	**<0.001**	5.01 (2.71–9.25)	0.53 (0.28–1.03)
Depression, anxiety and substance use (incl. self-report)	15 (11)	22 (2)	28 (19)	**<0.001**	8.14 (4.12–16.09)	0.54 (0.27–1.06)

(Continues)

TABLE 3 (Continued)

Characteristic	Off-label group ($n = 137$) *N* (%)	Comparison 1: Non-psychotic mental illness, no APs ($n = 1478$) *N* (%)	Comparison 2: Psychosis or bipolar disorder, with prescription and purchase of APs ($n = 151$) *N* (%)	*p*-Value	Off-label group vs. Comparison 1 OR (95% CI)	Off-label group vs. Comparison 2 OR (95% CI)
Somatic illnesses						
Diabetes mellitus	4 (3)	51 (4)	12 (8)	**0.019**	0.84 (0.30–2.36)	0.35 (0.11–1.11)
Diabetes mellitus, type 1	0	16 (1)	0	0.217	0 (0.00-)	-
Diabetes mellitus, type 2	4 (3)	42 (3)	12 (8)	**0.006**	1.03 (0.36–2.91)	0.35 (0.11–1.11)
Diseases of nervous system	52 (38)	426 (29)	42 (28)	0.073	1.51 (1.05–2.17)	1.59 (0.97–2.61)
Epilepsy	11 (8)	32 (2)	5 (3)	**0.001**	3.95 (1.94–8.01)	2.55 (0.86–7.53)
Diseases of circulatory system	39 (29)	413 (28)	43 (29)	0.982	1.03 (0.70–1.51)	1.00 (0.60–1.67)
Diseases of musculoskeletal system and connective tissue	85 (65)	839 (57)	65 (43)	**0.002**	1.25 (0.87–1.79)	2.16 (1.35–3.47)
Asthma or chronic obstructive pulmonary disease	12 (9)	140 (10)	21 (14)	0.192	0.92 (0.50–1.70)	0.59 (0.28–1.26)
Developmental disorder	2 (2)	12 (1)	4 (3)	0.087	1.81 (0.40–8.17)	0.54 (0.10–3.02)
Family history of mental disorders						
Parental psychosis	11 (8)	109 (7)	25 (17)	**0.001**	1.18 (0.83–1.68)	0.64 (0.40–1.02)
Non-psychotic psychiatric disorder	60 (44)	587 (40)	83 (55)	**0.001**	1.10 (0.58–2.01)	0.44 (0.21–0.93)

Note: Statistically significant ($p < 0.05$) *p*-values are in bold. OR = Odds ratio. 95% Cl = 95% confidence interval. SD = standard deviation. N.A.= not applicable.

*No diagnosis in national registers.

**All the individuals who had a diagnosis of psychosis or bipolar disorder were excluded from the off-label group and the comparison group 1.

TABLE 4 Number of persons using different antipsychotics

	Off-label group ($n = 137$)		Comparison 2: Psychosis or bipolar disorder, with prescription and purchase of APs ($n = 151$)	
Name of the drug	***n***	**%**	***n***	**%**
Atypical antipsychotics				
Quetiapine	88	64	78	52
Quetiapine depot	3	2	21	14
Olanzapine	5	4	63	42
Risperidone	12	9	61	40
Aripiprazole	1	1	32	21
Other atypical antipsychotics	0	0	24	16
Typical antipsychotics				
Levomepromazine	9	7	31	21
Perphenazine	20	15	47	31
Other typical antipsychotics	30	22	89	59

more likely to have a higher socioeconomic status compared with comparison group 2 [OR 2.01 (1.21–3.32)]. In comparison group 2, 66 members (44%) had a diagnosis of schizophrenia and 46 members (31%) had a diagnosis of bipolar disorder (Table 2). Members of the off-label group were less likely to be diagnosed with non-psychotic depression [OR 0.44 (0.25–0.78)], borderline personality disorder [OR 0.35 (0.14–0.86)], a substance abuse disorder [OR 0.60 (0.37–0.99)] and other non-psychotic mental disorders [OR 0.30 (0.17–0.52)] than members of comparison group 2. Morbidity was lower in the off-label group than in comparison group 2. Anxiety and stress-related disorders and substance abuse disorder comorbidity were less likely in the off-label group than in comparison group 2 [OR 0.54 (0.32–0.91)]. Diseases of the musculoskeletal system and connective tissue were more likely in the off-label group than in comparison group 2 [OR 2.16 (1.35–3.47)]. The off-label users were less likely to have a family history of non-psychotic psychiatric disorder [OR 0.44 (0.21–0.93)] (Table 3). Again, the similarity between the off-label group and comparison group 2 indicates that the clinical picture of the diseases or disorders is more severe in the off-label group than in comparison group 1.

4 | DISCUSSION

4.1 | Main results

In this sample, persons having a prescription and who had purchased APs off label had more psychiatric and somatic morbidity than persons with non-psychotic mental disorders who did not use APs. They also consumed more alcohol and smoked more often, had a lower level of education and socioeconomic status, and were less likely to be married than those with non-psychotic mental illness, but who did not have prescription and purchase of APs. There were less significant differences between individuals using APs off label compared with individuals with psychosis or bipolar disorder who used APs, though persons with psychosis or bipolar disorder had markers of more morbidity and a lower level of education and sociodemographic status.

4.2 | Comparison with previous studies

The AP off-label prescribing is common.[9] In Finland in 2019, 202,528 individuals used AP medication.[22] Nevertheless, only 35% received special reimbursement for their prescriptions because of psychosis or an equally severe mental disorder diagnosis. It can be assumed that most of the remaining individuals who had not received special reimbursement for prescriptions were using APs off label. Based on a systematic review,[9] the off-label prescribing rate was most frequently between 40% and 75% of AP prescriptions. The second-generation APs were more frequently prescribed off-label, and quetiapine was the most used AP in off-label indications, similarly as in our study. Also, Højlund et al[23] found that quetiapine was the most used AP, comprising 58% of all AP use. Their group also found that quetiapine use, particularly low-dose quetiapine use, has increased in the last 20 years.[5]

In our study, belonging to AP off-label group was associated with a less privileged socioeconomic status.

Dennis et al[24] studied 320 individuals who used APs and compared them to individuals not using APs. They found that the use of APs was associated with a lower education level and higher comorbidity. In their study sample, 52% of the persons who used APs had only received a college diploma as the highest educational level, whereas 36% of the comparison group had received a college diploma as the highest educational level. Like our study, Bauer et al[25] found that married individuals tend to have less off-label AP use.

In our study, individuals who had been prescribed APs off label had several markers of poor health. For example, compared with individuals with a non-psychotic mental disorder but who did not use APs, they more often had more than one mental health diagnosis. Among individuals in AP off label group, 34% had a diagnosis of depression and anxiety, compared with 18% among individuals with a non-psychotic mental disorder but who did not use APs. In addition, of the off-label group members, 23% had a diagnosis of depression and substance abuse, whereas in comparison group 1, the percentage was 5%. These results are in line with previous studies: Psychiatric comorbidities such as depression, anxiety, and sleep disorders[25] are common in individuals using APs off label. In addition, comorbidity and polypharmacy are more common in AP users[24] (Table S1).

Carton et al[9] found that some diagnoses were common among persons with APs off-label, such as mood disorders, anxiety disorders, insomnia, borderline personality disorders, OCD, PTSD, and substance abuse disorders. This may partly reflect the evidence for the efficacy of some AP on some non-psychotic and non-bipolar mental disorders. Based on a large scale systematic review by Maglione et al,[11] some APs are effective in some off-label conditions. There is evidence to demonstrate that quetiapine is an effective treatment for anxiety (GAD) and MDD. There is also some evidence that quetiapine might be effective as a treatment for OCD, borderline personality disorder and PTSD. Maglione et al[11] also studied the off-label efficacy of aripiprazole, olanzapine, risperidone, and ziprasidone, that had low or moderate efficacy for social phobia, hyperactivity disorder, OCD as an augmentation with antidepressants, borderline personality disorder and PTSD.

Only a few previous studies have examined the connection between smoking,[24] alcohol consumption[26] and AP off-label use. Dennis et al[24] identified 320 persons who had been prescribed APs (on- and off-label) in their study population. They found that persons with prescription of AP off-label tend to have a lower level of education, more medication prescriptions and were more often obese than individuals without prescription of APs off label. Our study population is from the general population, which represents an average working-age population and found a strong association between multiple mental disorders and receiving AP off-label prescription. Epilepsy was highly associated with AP off-label use. The study population of Bauer et al[25] comprised U.S. veterans. The study population was large, but over 92% were male. In their study depression, substance abuse disorder, anxiety disorders, hyperlipidaemia and obesity were associated with AP off-label use. In another sample of veterans,[26] most of the off-label users had a diagnosis of PTSD, mild depression, or alcohol dependence.

4.3 | Clinical implications

One of the most common conditions for APs off label use are insomnia and anxiety.[9,27] In Finland, the primary treatment for generalised anxiety disorder (GAD) is psychotherapy and antidepressants. The Finnish care guidelines only recommend APs as a secondary treatment for GAD.[28] They do not recommend APs for the treatment of insomnia. Using APs as a treatment for insomnia is recommended only in accordance with specific criteria.[29]

The UK National Institute for Health and Care Excellence (NICE) has its own treatment guidelines for anxiety and depression.[30] In the anxiety guidelines, NICE states that APs should not be the primary care option for treating anxiety disorder. According to NICE's guidelines, APs as an augmentation treatment have shown little evidence of effectiveness in treating anxiety. In the depression guidelines, NICE approves of the use of APs as an augmentation treatment.[31] APs as a monotherapy for depression also showed promising results, but there is still a lack of evidence about their effectiveness. The U.S. Department of Veteran Affairs created its own guidelines for treating insomnia.[32] According to its guidelines, APs should not be a part of treating insomnia because of the lack of evidence and potential safety concerns.

Our study shows that persons using APs off-label have poorer mental and physical health markers than those with non-psychotic mental disorder and who do not use antipsychotics. It may be that for some of the subjects, APs have been prescribed to treat severe illness with plausible long treatment history.[33] APs may have been prescribed to for example treatment-resistant depression, where APs have shown effectiveness as an augmentation treatment.[34] We were not able to analyse the reasons for prescriptions in this sample. Other studies have shown that APs are prescribed off-label for variable reasons. For example, quetiapine may be prescribed to avoid long-term use and potential harms of benzodiazepines[27,35] because of a lack of psychosocial treatment options[27] and in complex mental health problems and

psychosocial needs.[35] Based on an interview with family physicians, quetiapine is being prescribed to patients who do not respond to first-line therapies, those who have multiple psychiatric diagnoses, or those with complex psychological or social histories.[35] There is some evidence that one of the important reasons for increased use of APs off-label, for example, in insomnia is the lack of available treatment options,[27,36] which may apply to off-label use more broadly.

The doses of APs in off-label use are usually relatively small.[27,35,37] However, safety concerns have been presented regarding the off-label use of APs[9,11] and small doses of quetiapine.[38–40] For example, in a clinical trial in an adult sample, a relatively low dose of quetiapine of ca. 117 mg/d significantly increased blood pressure, body weight, body mass index, and fasting glucose after 2 years of use.[38] In another study with quetiapine dosing up to 100 mg/d, body weight increased after 6 and 12 months of use.[40] However, in a large Danish register study, low-dose quetiapine did not associate with excess risk of type 2 diabetes in comparison with selective serotonin reuptake inhibitors.[41] The long-term effects of low doses of APs in off-label use need further exploration. In addition, the potentially harmful effects of even small doses of AP should be acknowledged in clinical practice, and proper follow-up and monitoring of long-term effects and for example, metabolic effects should be done more systematically.[27]

4.4 | Strengths and limitations

Our study has some limitations. The sample size of the off-label group was relatively small even though all the AP off-label prescriptions during the follow-up were included in the study. Medication data were only available for a limited though relatively long period (14 years). Medication data did not include information on whether individuals had actually used the prescribed medication. However, the use is very probable since the SII data only include individuals who purchased their medication from a pharmacy. The dose, duration or purpose of the medication was not included in the data. However, information about the prescription and the purchasing of medication alone is important as it reflects the need for the off-label use of AP recognised by physician. The causality between AP off-label use and background variables is not known and temporality can also be unclear in some cases. Although this study used many national registers, information about psychiatric morbidity does not include information about the severity of symptoms. The registers do not cover occupational health visits, and the health centre register is available only from year 2011. Therefore, we were not able to study the prevalence of less severe disorders, such as primary insomnia, in this sample. The lack of diagnoses from occupational health care and health centres probably explains why the number of insomnia diagnoses in this sample was so low. The register information on marital status divided the sample into married, registered relationships, divorced or never married, but there was no response option for cohabiting. We studied psychiatric morbidity during a period (from 1 January 1985 to the start of the 46-year study) when one individual might have received various psychiatric diagnoses from different organisations (i.e., health centres, occupational health, or hospitals). In both the 31- and 46-year-study questionnaires, the questions about self-reported diagnoses did not have bipolar disorder as a response option, so it could be that some individuals may have reported bipolar disorder as another mental disorder. However, the possibility of bipolar disorders being reported as another mental disorder is small, and this possible misclassification will most likely not affect the results.

Despite these limitations, the study has many strengths. First, only a few previous studies have been conducted on the characteristics of AP off-label users. This study examined factors associated with off-label use at the subject level, providing valuable information for the development of current clinical practices. The data included several variables describing characteristics and predictors of antipsychotic off-label use compared with previous studies, making it possible to describe AP off-label users more accurately than previous studies. The data were gathered prospectively from multiple comprehensive national registers and questionnaires and include various variables from the participants' backgrounds including family history, socioeconomic class, education, morbidity, and prescription history. The study population was an unselected non-clinical general population. We were able to compare off-label users to two comparison groups, i.e. individuals with non-psychotic mental disorders but who did not use APs and individuals with psychosis or bipolar disorder. An analysis of three groups with various variables allowed us to describe off-label users more accurately than previous studies. The prescription data included 14 years of prescribed medications. Information about psychiatric and somatic diagnoses covered the entire period of adulthood from 18 to 46 years.

5 | TO CONCLUDE

Based on this general population adult sample, individuals with prescription and purchase of APs off-label had

a higher mental and somatic morbidity and poorer socioeconomic status than individuals with non-psychotic mental disorders without prescription and purchase of APs. This highlights the need for further studies on long-term effects of AP in this group and analyses on effective on-label medication and psychosocial treatments for severe non-psychotic disorders.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13472.

DATA AVAILABILITY STATEMENT

NFBC data is available from the University of Oulu, Infrastructure for Population Studies. Permission to use the data can be granted for research purposes via the electronic material request portal. Regarding the use of data, we follow the EU General Data Protection Regulation (679/2016) and the Finnish Data Protection Act. The use of personal data is based on the cohort participants' written informed consent during their latest follow-up study, which may result in limitations regarding its use. Please contact the NFBC project centre (nfbcprojectcenter@oulu.fi) and/or visit the cohort website (https://www.oulu.fi/nfbc) for further information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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