



Use of antidepressants and mood stabilizers in persons with first-episode schizophrenia

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Received: 8 August 2019 / Accepted: 6 January 2020 / Published online: 15 January 2020
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Abstract

Purpose Antipsychotics are first-line treatment of schizophrenia. They are often accompanied by adjunctive treatments, such as antidepressant (AD) or mood stabilizer (MS), although there is only limited information of their use in first-episode schizophrenia. This study aimed to investigate AD and MS initiation and factors associated with initiation in persons with first-episode schizophrenia.

Methods Register-based data was utilized to identify persons who received inpatient care due to schizophrenia during 1996–2014 in Finland and who did not use AD or MS at the time of first inpatient care diagnosis of schizophrenia ($N = 7667$, mean age 40.2, SD 18.2). Drug purchase data (1995–2017) was obtained from the National Prescription register and modelled with PRE2DUP method. Initiations of AD and MS use were followed up 3 years from first schizophrenia diagnoses. Cox proportional hazard models were used to investigate factors associated with AD or MS initiation.

Results Among persons with first-episode schizophrenia, 35.4% initiated AD and 14.1% initiated MS use within three years from diagnoses. Female gender, younger age, and benzodiazepine use were associated with higher risk of AD and MS initiation. The number of previous psychoses was associated with decreased risk of AD and increased risk of MS initiation.

Conclusion Clinical guidelines rarely recommend the use of AD or MS as adjunctive treatment in persons with schizophrenia. However, this population is often treated with AD or MS. More studies are needed to evaluate benefits and risks of these medications as adjunctive treatment of schizophrenia.

Keywords Antidepressants · Antipsychotics · Mood stabilizers · Schizophrenia

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00228-020-02830-2>) contains supplementary material, which is available to authorized users.

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Introduction

Antipsychotics are the first-line treatment of schizophrenia [1, 2]. Antipsychotics affect especially positive symptoms, whereas for negative symptoms and cognitive impairment, they are less effective [3]. Antidepressant (AD) or mood stabilizer (MS) use as adjuvants to antipsychotics has been investigated in treatment for symptoms such as depressive and negative symptoms [4] and aggression [5], but they are rarely recommended in clinical guidelines due to lack of high quality evidence of their efficacy [3, 6, 7]. Evidence on benefits in clinical trials is mixed which was represented by a recent study reporting that add-on citalopram was associated with reduced levels of negative symptoms but had no impact on depressive symptoms [8]. In a recent observational study, antidepressant use was associated with lowered risk of psychiatric hospitalization and emergency department visits, whereas mood stabilizers had no impact on these outcomes [9]. In that study, mood stabilizer use was associated with somewhat

increased risk of mortality, but antidepressant use was not. On the other hand, a previous observational study found cumulative antidepressant exposure to be associated with lower mortality risk compared with no antidepressant use in patients with schizophrenia [10].

The prevalence of AD and MS use in persons with schizophrenia has been previously studied. In United States, Chakos et al. found that 31% persons with schizophrenia received AD medication, whereas 3% used lithium and 12% other mood stabilizer [11]. A study conducted among US Department of Veteran Affairs (VA) healthcare patients reported annual prevalence of AD use as 37.4% [12]. A more recent US study reported prevalence as high as 40.6% AD use and 32.4% MS use as adjunctive treatment with antipsychotics [13]. Similarly high prevalence of AD use was found in persons with schizophrenia in Sweden, namely, 38.8% [10]. Karagianis and colleagues reported adjunctive use of AD and MS in different continents, and the prevalence of AD use varied regionally from 15.2% to 24.1%, and MS use varied from 8.7% to 19.9% [14].

There is limited amount of studies concerning antidepressants and mood stabilizers as adjunctive pharmacotherapy for first-episode schizophrenia, and no studies assessing initiation of antidepressant or mood stabilizer use after the diagnoses. The objectives of our study were to investigate antidepressant and mood stabilizer use and factors associated with their initiation in first-episode schizophrenia.

Methods

Study population

The source population included all persons who received inpatient care due to schizophrenia from 1972 to 2014 in Finland (ICD-10 diagnoses F20 and F25, ICD-9 and ICD-8 diagnoses 295). This information was obtained from the Hospital Discharge register maintained by National Institute of Health and Welfare. For this study, 8342 persons with a first inpatient diagnoses of schizophrenia, without antipsychotic use during preceding year (short as first-episode schizophrenia) during 1996–2014 were included (mean age 40.6, SD 18.3, 56.3% males), and they formed the study population. More information on this cohort was added from several registers: drug purchase data (1995–2017) was obtained from the National Prescription register maintained by the Social Insurance Institution, all hospital care periods from Hospital Discharge register (1972–2017) and causes of death (1972–2017) from the National Death register.

Exposure

Drug purchase data included all reimbursed prescription drug purchases in community pharmacies in Finland and were

categorized according to Anatomic Therapeutic Chemical (ATC) classification [15], and by mechanism of action. In this study, the focus was on the use of antidepressants (N06A) and mood stabilizers. Studied antidepressant groups were nonselective monoamine reuptake inhibitors (N06AA), selective serotonin reuptake inhibitors (SSRIs, N06AB), monoamine oxidase A inhibitors (N06AG), and other antidepressants (N06AX). Within other antidepressants, mirtazapine (N06AX11) and serotonin-norepinephrine reuptake inhibitors (SNRIs) were also examined separately. SNRI group included venlafaxine (N06AX16), milnacipran (N06AX17) and duloxetine (N06AX21). Mood stabilizers were defined as carbamazepine (N03AF01), valproic acid (N03AG01) and lamotrigine (N03AX09). Lithium (N05AN01) was included in mood stabilizers.

The register-based drug purchase data does not provide information on the duration of drug use. To investigate the duration, we used the PRE2DUP method, developed by our research group [16]. PRE2DUP estimates drug use periods based on the sliding average of daily doses, purchased amount, and parameters assigned for drug packages which control the joining of purchases. In addition to these, PRE2DUP considers changes of doses, possible inpatient care (wherein drug use is not recorded on the registers) and stockpiling of drugs. PRE2DUP and the validity of this method are described in detail in previous studies [16–18].

Study inclusion criteria

The inclusion criteria for this study were that the person was diagnosed with schizophrenia in 1996 or after and did not use antipsychotics within a year before the first diagnosis. Prevalence of AD and MS use was assessed within this group ($N = 8342$). For identification of new antidepressant and mood stabilizer users, persons who had ongoing AD and/or MS use at the index date (discharge from the first schizophrenia-related hospitalization) were excluded ($N = 675$) (Supplementary Fig. 1). The final cohort consisted of 7667 persons, who were followed up for AD and MS initiation for 3 years after the index date.

Outcomes

The main outcome was initiation of AD or MS use. We also described initiations of AD and MS subgroups by ATC classification and/or by mechanism of action.

Covariates

Factors associated with the initiation of AD or MS were separately investigated for these two groups. These factors included age, gender, previous suicidal behaviour, substance abuse and the number of previous hospitalizations due to

psychoses. In addition, comorbid conditions including cardiovascular diseases (CV-diseases), cancer, diabetes, asthma, post-traumatic stress disorder (PTSD) and lipidemias were assessed. We also assessed use of analgesics, anticholinergic anti-Parkinson drugs (for extrapyramidal symptoms of antipsychotics), benzodiazepines and benzodiazepine-related drugs (z-drugs). Detailed definitions of comorbidities are presented in Supplementary Table 1.

Statistical analysis

Prevalence of AD and MS use, alone or in combination, was assessed as point prevalence every 6 months, from 3 years before and until 3 years after the index date. For initiations of AD and MS use after the index date, the follow-up ended 3 years after index date, death, or 31st of December 2017, whichever occurred first. Kaplan-Meier analyses were performed to investigate time to the initiation of adjunctive pharmacotherapy. The association between covariates and AD or MS initiation was investigated with Cox proportional hazard models. Associations were reported as unadjusted and adjusted Hazard Ratios (HRs) with 95% confidence intervals (CIs). Data analyses were performed with SAS for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics of the study

The data for this study was collected and combined from registers utilizing personal identification numbers, and no contact was made with the participants of the study. Permissions were granted by pertinent institutional authorities at the Finnish National Institute for Health and Welfare (permission THL/1466/6.02.00/2013), The Social Insurance Institution of Finland (34/522/2013), and Statistics Finland (TK53–305-13). Before submission to the researchers, the data was de-identified, and no informed consent from the participants was required according the Finnish legislation.

Results

The mean age of the study population was 40.2 years (SD 18.2) at the first hospitalization, and 56.8% were males. Within 3 years of follow-up, 18.3% had one psychiatric readmission and 28.9% had more than one, whereas 52.9% was not readmitted. Prevalence of AD (6.4–8.4%), MS (1.3–1.7%) and their concomitant use (0.6–0.7%) remained on a constant level from 3 years before until the first schizophrenia diagnoses (Fig. 1). After diagnoses, prevalence of AD and MS use increased and stabilized at a higher level within 1–1.5 years. Three years after the diagnoses, 19.1% used AD, 6.8% MS and 2.7% used both.

Within 3 years of follow-up, 2713 persons (35.4%) initiated AD use and 1084 persons (14.1%) initiated MS use (Fig. 2). The most frequently initiated subgroup of antidepressants was SSRIs (26.3%), and valproic acid was the most often initiated mood stabilizer (8.5%). The mean time to AD initiation was 2.15 years (95% CI 2.13–2.18) and 2.66 years (95% CI 2.64–2.68) to MS initiation (Supplementary Fig. 2).

Both antidepressant and mood stabilizer initiators were younger than those who did not initiate these drugs (Table 1). Males initiated MS use more often than females (53.8% of initiations, $p = 0.0289$). Among AD initiators, benzodiazepine and z-drug use was more common than among non-initiators, whereas MS initiators used more frequently antidepressants, and benzodiazepines than non-initiators. Suicidal behaviour was more common in both AD and MS initiators, and substance abuse was more common among MS initiators than non-initiators. Considering comorbidities, CV-diseases were more common in those who did not initiate MS or AD use compared to initiators. We also examined ten most commonly used antipsychotics. Among both AD and MS initiators, the most used antipsychotic was olanzapine, followed by risperidone and clozapine except for MS initiators, where clozapine was more commonly used than risperidone.

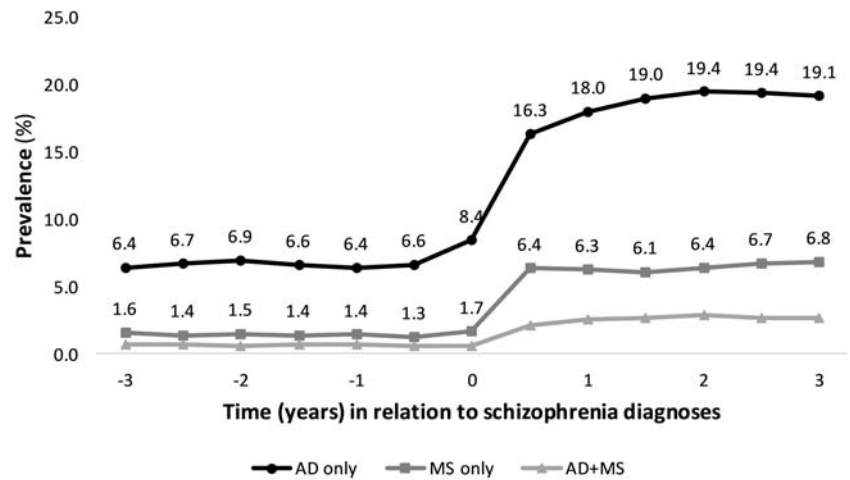
Female gender and younger age were associated with an increased risk of initiating AD (Table 2). Use of benzodiazepines (aHR 1.78, 95% CI 1.58–2.01) and z-drugs (aHR 1.28, 95% CI 1.07–1.54) were associated with AD initiation. Higher number of previous psychoses requiring inpatient care was associated with a reduced risk of initiating antidepressant (one previous psychosis: aHR 0.82, 95% CI 0.74–0.90, two or more psychoses: aHR 0.71, 95% CI 0.64–0.79) compared to those who had no previous psychoses.

As with antidepressants, female gender and younger age were associated with increased risk of MS initiation (Table 2). Use of antidepressants (aHR 1.22, 95% CI 1.01–1.48), benzodiazepines (aHR 1.37, 95% CI 1.12–1.68) and analgesics (aHR 1.39, 95% CI 1.13–1.72) was also associated with MS initiation. Previous suicidality was also associated with MS initiation (HR 1.30, 95% CI 1.03–1.65). Considering the number of previous hospitalizations due to psychoses, those who had one or several psychoses were at higher risk of MS initiation compared to those who did not have previous psychosis (aHR 1.22, 95% CI 1.05–1.42 and 1.22, 95% CI 1.04–1.42, respectively).

Discussion

Our study showed that slightly more than one third of persons with first-episode schizophrenia initiated adjunct AD and approximately 15% initiated MS medication within 3 years of follow-up. Factors associated with both AD and MS initiation were younger age, female gender and use of benzodiazepines.

Fig. 1 Point prevalence of antidepressant (AD) only, mood stabilizer (MS) only and their concomitant use (AD+MS) from 3 years before and until 3 years after the first schizophrenia diagnoses (time point zero)



The number of previous hospital-treated psychosis was associated with decreased risk of AD and increased risk of MS initiation.

According to the best of our knowledge, no previous study has assessed AD and MS initiations among persons with first-episode schizophrenia. However, prevalence of AD and MS use reported in previous studies has been somewhat similar [10, 11]. Olsson and colleagues reported slightly higher AD use and considerably higher MS use [13]. On the other hand, a study considering different continents reported clearly lower prevalence of AD use throughout the study but showed large regional differences in AD and MS use [14].

We found that female gender and younger age were associated with initiation of adjunctive medication. A previous study found that mood stabilizer use was associated with younger age, aggression and positive symptoms [19]. It is possible that mood stabilizers in our study were initiated for agitation and aggressive behaviour as there is some evidence on effectiveness of mood stabilizers for these symptoms [20]. Antidepressant initiations might reflect prevalence of negative and depressive symptoms, even though evidence of their effectiveness for these symptoms is controversial [4, 6]. More

common AD initiation in women is likely related to the fact that women are more likely to present depressive symptoms than men [21, 22]. Both AD and MS initiation was associated with benzodiazepine use. Benzodiazepine use may be a marker of anxiety symptoms but their use is controversial and often avoided because benzodiazepine use is associated with risk of dependence, tolerance and withdrawal effects [23]. Thus, AD and MS initiation may be an attempt to treat anxiety symptoms instead of benzodiazepines.

We also found that higher number of previous psychoses was associated with MS initiation, but an inverse association was found for AD initiation. This may be explained by use of MS (such as lithium) to control aggressive behaviour [24] and florid positive symptoms seen especially in schizoaffective disorder, resulting into recurrent hospitalizations. Patients with depressive and negative symptoms may be less frequently hospitalized, and they may receive more often antidepressive add-on treatment.

Persons initiating antipsychotic medication were aged roughly 39 years. This mean age is relatively high but in line with a previous study on first-episode schizophrenia cohort in Sweden [25]. According to a previous study,

Fig. 2 Initiations of mood stabilizer (MS) and antidepressant (AD) subgroups within 3 years after antipsychotic initiation. TCA tricyclic antidepressant, SSRI selective serotonin reuptake inhibitor, SNRI serotonin-norepinephrine reuptake inhibitor. Percentages of subgroups may not add up to total MS or AD category percentage because some persons initiated with multiple drugs or drug categories

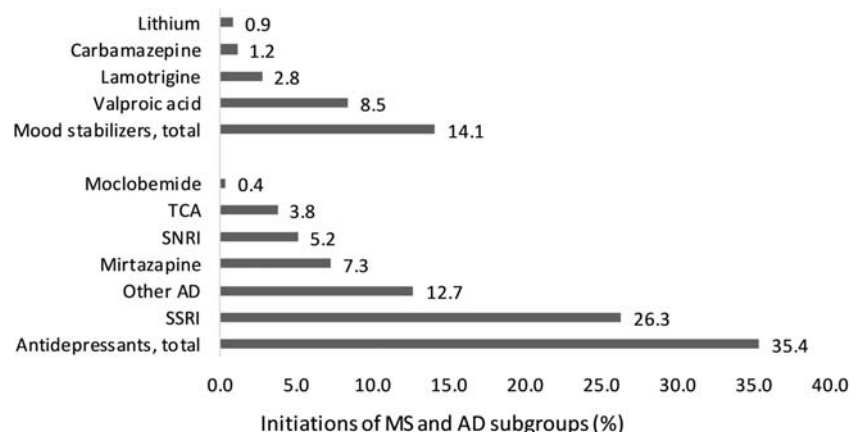


Table 1 Characteristics of antidepressant and mood stabilizer initiators and non-initiators

	Antidepressant % (N)			Mood stabilizer % (N)		
	Initiator (N = 2713)	Non- initiator (N = 4954)	P value	Initiator (N = 1084)	Non- initiator (N = 6583)	P value
Age categories			< 0.0001			< 0.0001
≤ 20	7.7 (210)	5.3 (261)		9.4 (102)	5.6 (369)	
21–30	35.5 (963)	26.8 (1328)		34.7 (376)	29.1 (1915)	
31–40	21.3 (578)	19.2 (949)		23.2 (251)	19.4 (1276)	
41–50	15.3 (416)	15.6 (773)		16.0 (173)	15.4 (1016)	
51–60	9.7 (263)	13.0 (643)		9.7 (105)	12.2 (801)	
> 60	10.4 (283)	20.2 (1000)		7.1 (77)	18.3 (1206)	
Female gender	44.1 (1195)	42.7 (2115)	0.2523	46.2 (501)	42.7 (2809)	0.0289
Antidepressant				12.4 (134)	8.7 (573)	0.0001
Mood stabilizer	4.0 (108)	2.7 (135)	0.0027			
Anticholinergic anti-Parkinson drugs	1.6 (44)	1.1 (55)	0.0578	1.4 (15)	1.3 (84)	0.7709
Benzodiazepines	12.7 (345)	6.6 (325)	< 0.0001	11.4 (124)	8.3 (546)	0.0007
Z-drugs	4.9 (132)	3.5 (171)	0.0024	4.2 (46)	3.9 (257)	0.5949
Analgesics	9.2 (250)	8.2 (404)	0.1121	9.8 (106)	8.3 (548)	0.1122
Substance abuse	13.8 (375)	13.5 (668)	0.6795	16.2 (176)	13.2 (867)	0.0064
Suicidality	6.2 (169)	4.7 (231)	0.0032	7.6 (82)	4.8 (318)	0.0002
CV-diseases	9.6 (259)	13.4 (663)	< 0.0001	7.7 (83)	12.7 (839)	< 0.0001
Cancer	1.6 (42)	2.4 (118)	0.0146	0.9 (10)	2.3 (150)	0.0038
Diabetes	3.0 (82)	4.5 (224)	0.0013	2.8 (30)	4.2 (276)	0.0263
Asthma	3.5 (96)	3.1 (155)	0.3350	3.7 (40)	3.2 (211)	0.4059
PTSD	0.4 (11)	0.3 (15)	0.4596	0.5 (5)	0.3 (21)	0.4554
Lipoprotein disorders	2.7 (74)	3.4 (168)	0.1120	1.9 (21)	3.4 (221)	0.0132
Previous psychoses			< 0.0001			0.0051
None	66.2 (1796)	59.1 (2930)		57.2 (620)	62.4 (4109)	
1	18.7 (506)	20.8 (1032)		22.3 (242)	19.7 (1296)	
≥ 2	15.2 (411)	20.0 (992)		20.5 (222)	17.9 (1181)	
Ten most commonly used antipsychotics at the time of AD or MS initiation						
Olanzapine	19.0 (515)			18.0 (195)		
Risperidone	13.3 (360)			10.6 (115)		
Clozapine	11.6 (316)			14.8 (160)		
Quetiapine	4.8 (131)			5.6 (61)		
Perphenazine	2.8 (77)			2.1 (23)		
Aripiprazole	1.9 (51)			1.3 (14)		
Risperidone LAI	1.8 (49)			1.5 (16)		
Perphenazine LAI	1.2 (33)			0.7 (8)		
Haloperidol	1.0 (27)			1.1 (12)		
Zuclopenthixol LAI	1.0 (27)			1.2 (13)		
Other AP	5.8 (157)			7.0 (76)		
AP polytherapy	19.2 (521)			23.1 (250)		
No AP	16.5 (449)			13.0 (141)		

CV-diseases cardiovascular diseases, PTSD post-traumatic stress disorder, Lipoprotein disorders: Disorders of lipoprotein metabolism and other lipidemias, LAI long-acting injection, AP polytherapy: two or more antipsychotics in use simultaneously

Finnish inpatient care diagnoses of schizophrenia have high validity (no false positive cases), but the register data may lack

some persons fulfilling the diagnostic criteria for schizophrenia [26]. This likely reflects diagnostic delay in setting the final

Table 2 Factors associated with antidepressant and mood stabilizer initiation

	Antidepressants						Mood stabilizers					
	Unadjusted			Adjusted			Unadjusted			Adjusted		
	HR	Lower CI	Upper CI	HR	Lower CI	Upper CI	HR	Lower CI	Upper CI	HR	Lower CI	Upper CI
Age categories												
≤ 20	2.15	1.79	2.56	2.56	2.11	3.11	3.65	2.71	4.90	4.03	2.92	5.55
21–30	2.03	1.78	2.32	2.43	2.08	2.83	2.73	2.13	3.48	2.97	2.25	3.91
31–40	1.79	1.55	2.06	2.13	1.81	2.49	2.75	2.13	3.55	2.85	2.16	3.77
41–50	1.62	1.40	1.89	1.88	1.60	2.22	2.41	1.84	3.15	2.44	1.83	3.25
51–60	1.31	1.11	1.55	1.45	1.21	1.72	1.92	1.43	2.58	1.91	1.41	2.59
> 60 (reference)												
Female gender	1.06	0.98	1.14	1.19	1.10	1.29	1.15	1.02	1.30	1.33	1.17	1.51
Mood stabilizers	1.37	1.13	1.66	1.18	0.97	1.43	NA			NA		
Antidepressants	NA			NA			1.44	1.20	1.72	1.22	1.01	1.48
Anticholinergic anti-Parkinson drugs	1.35	1.00	1.82	1.11	0.82	1.51	1.08	0.65	1.80	0.91	0.55	1.53
Benzodiazepines	1.82	1.63	2.04	1.78	1.58	2.01	1.43	1.19	1.73	1.37	1.12	1.68
Z-drugs	1.38	1.16	1.65	1.28	1.07	1.54	1.12	0.83	1.50	1.12	0.82	1.52
Analgesics	1.16	1.02	1.32	1.15	1.00	1.32	1.22	1.00	1.49	1.39	1.13	1.72
Substance abuse	1.03	0.92	1.15	1.00	0.90	1.13	1.25	1.06	1.47	1.16	0.98	1.38
Suicidality	1.27	1.09	1.48	1.17	0.99	1.37	1.55	1.24	1.94	1.30	1.03	1.65
CV-diseases	0.78	0.69	0.89	1.01	0.87	1.16	0.62	0.50	0.78	0.88	0.69	1.13
Cancer	0.77	0.57	1.05	1.09	0.80	1.49	0.45	0.24	0.84	0.69	0.37	1.30
Diabetes	0.76	0.61	0.94	0.91	0.72	1.16	0.70	0.49	1.01	1.00	0.68	1.47
Asthma	1.10	0.89	1.34	1.11	0.90	1.36	1.17	0.85	1.60	1.23	0.89	1.68
PTSD	1.15	0.64	2.08	0.89	0.49	1.62	1.40	0.58	3.36	0.99	0.41	2.39
Lipoprotein disorders	0.86	0.69	1.09	1.21	0.94	1.56	0.61	0.40	0.94	1.02	0.64	1.62
Previous psychoses												
0 (reference)												
1	0.83	0.75	0.91	0.82	0.74	0.90	1.22	1.06	1.42	1.22	1.05	1.42
≥ 2	0.71	0.64	0.79	0.71	0.64	0.79	1.22	1.05	1.42	1.22	1.04	1.42

CV-diseases cardiovascular diseases, PTSD post-traumatic stress disorder, Lipoprotein disorders: Disorders of lipoprotein metabolism and other lipidemias

diagnoses, which is also supported by the fact that a large proportion of persons had used antipsychotics before their first diagnoses [27].

Our study has certain strengths and limitations. Finnish nationwide registers provide reliable information on schizophrenia, and comprehensive data of dispensed medications. Register-based studies usually have also limitations. The utilized registers, for example, do not offer data of indications of use or severity of symptoms. In addition, medication use during inpatient care is not recorded in the registers, and thus we lacked this information. The utilized registers include only persons diagnosed in inpatient care with schizophrenia and lack data on schizophrenia patients diagnosed only in outpatient care. However, persons with schizophrenia tend to be admitted into inpatient

care at re-emergence of psychosis, and for this reason, this has only limited impact on the generalizability of our study. We lacked data on primary non-adherence, i.e., prescribed drugs that are never dispensed, and doses.

In conclusion, persons with first-episode schizophrenia relatively often use adjunctive AD and/or MS medication. As there is limited evidence of their effectiveness, more studies are needed to investigate the benefits and risks of these adjunctive medications.

Acknowledgements Open access funding provided by University of Eastern Finland (UEF) including Kuopio University Hospital.

Author contributions Conceptualization: Arto Puranen, Heidi Taipale. Methodology: Arto Puranen, Heidi Taipale, Marjaana Koponen, Antti Tanskanen. Formal analysis and investigation: Arto Puranen, Heidi

Taipale. Writing - original draft preparation: Arto Puranen. Writing - review and editing: All authors. Funding acquisition: Heidi Taipale, Jari Tiihonen. Critical revision of the manuscript for important intellectual content: All authors.

Funding This study was funded by the Finnish Ministry of Social Affairs and Health through the developmental fund for Niuvanniemi Hospital. HT and AP were funded by Academy of Finland (grants 315969, 320107). The funders of the study had no role in study design, data collection, data analysis, data interpretation, review or approval of the manuscript, or in the decision to submit the manuscript for publication.

Compliance with ethical standards

Conflict of interest Jari Tiihonen, Heidi Taipale and Antti Tanskanen have participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution. Jari Tiihonen reports personal fees from the Finnish Medicines Agency (Fimea), European Medicines Agency (EMA), Eli Lilly, Janssen-Cilag, Lundbeck, and Otsuka; is a member of advisory board for Lundbeck, and has received grants from the Stanley Foundation and Sigrid Jusélius Foundation. The other authors report no conflict of interest.

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