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Antipsychotic medications and sleep problems in patients with schizophrenia

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ABSTRACT

Background: Sleep problems are common and related to a worse quality of life in patients with schizophrenia. Almost all patients with schizophrenia use antipsychotic medications, which usually increase sleep. Still, the differences in subjective sleep outcomes between different antipsychotic medications are not entirely clear.
Methods: This study assessed 5466 patients with schizophrenia and is part of the nationwide Finnish SUPER study. We examined how the five most common antipsychotic medications (clozapine, olanzapine, quetiapine, aripiprazole, and risperidone) associate with questionnaire-based sleep problems in logistic regression analyses, including head-to-head analyses between different antipsychotic medications. The sleep problems were difficulties initiating sleep, early morning awakenings, fatigue, poor sleep quality, short (≤6 h) and long sleep duration (≥10 h).
Results: The average number of antipsychotic medications was 1.59 per patient. Clozapine was associated with long sleep duration (49.0 % of clozapine users vs 30.2 % of other patients, OR = 2.05, 95 % CI 1.83–2.30, $p < .001$). Olanzapine and risperidone were in head-to-head analyses associated with less sleep problems than patients using aripiprazole, quetiapine, or no antipsychotic medication. Aripiprazole and quetiapine were associated with more insomnia symptoms and poorer sleep quality. Patients without antipsychotic medications ($N = 159$) had poorer sleep quality than patients with antipsychotic use, and short sleep duration was common (21.5 % of patients using antipsychotics vs 7.8 % of patients using antipsychotics, OR = 2.97, 95 % CI 1.98–4.44, $p < .001$).
Conclusions: Prevalence of sleep problems is markedly related to the antipsychotic medication the patient uses. These findings underline the importance of considering and assessing sleep problems when treating schizophrenia patients with antipsychotics.

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1. Introduction

Sleep problems are common in patients with schizophrenia (Krystal, 2012). The sleep problems include both insomnia and hypersomnia symptoms, (Freeman et al., 2020; Laskemoen et al., 2019) and their importance is underlined by associations with worse outcomes, including more psychotic symptoms, worse life quality, functional abilities, and higher suicidality. (Li et al., 2016; Reeve et al., 2018; Ritsner et al., 2004; Waite et al., 2020) Simultaneously, most patients with schizophrenia use antipsychotic medications that impact their sleep. (Benson, 2015) In Finnish patients, clozapine, olanzapine, quetiapine, aripiprazole, and risperidone are the five most common antipsychotic medications in patients with schizophrenia. (Taipale et al., 2021).

Antipsychotic medications are generally, based on polysomnography studies, believed to increase sleep in patients with schizophrenia, leading to shorter sleep latency and longer sleep duration. (Benson, 2015; Monti et al., 2017) The evidence for increased sleep has been most consistent for clozapine and olanzapine, while quetiapine and risperidone have had mixed results. (Monti et al., 2017) No polysomnography studies have been conducted on aripiprazole.

This sedative impact is believed to alleviate insomnia symptoms, (Benson, 2015) but studies with systematic measurements of subjective sleep symptoms have been lacking. (Krystal et al., 2008) Many studies published to this have largely relied on adverse effect reporting, thus susceptible to underreporting, (Cascade et al., 2010; Loke et al., 2011) and have had undefined, or varying, insomnia or hypersomnia criteria, making comparisons between medications difficult. (Krystal et al., 2008; Lieberman et al., 2005; Miller et al., 2023).

In a recent meta-analysis that compared the adverse effect reports of insomnia symptoms in clozapine treatment to other antipsychotics found that using any other antipsychotic medication than clozapine was associated with reporting more insomnia symptoms. (Miller et al., 2023) The differences between other antipsychotics are not as clear. In the meta-analysis, olanzapine had the second-lowest rate of insomnia symptoms, followed by risperidone, and quetiapine, respectively. Aripiprazole was not included but has in previous clinical trials had a high rate of adverse reports of insomnia symptoms compared to other antipsychotics. (Krystal et al., 2008).

Antipsychotics can, because of their sedative impact, cause functionally impairing hypersomnia symptoms, including excessively long sleep duration (long SD) and daytime somnolence. (Fang et al., 2016; Tandon et al., 2020) Clozapine is viewed as the most sedative antipsychotic, and was in a systematic review the only antipsychotic categorized as highly somnolent. (Fang et al., 2016) Up to 50 % of clozapine users report somnolence as an adverse effect. (Krystal et al., 2008) In recent meta-analyses of antipsychotic efficacy, also quetiapine has had a strong sedative effect, followed by olanzapine, risperidone, and aripiprazole, respectively. (Huhn et al., 2019; Schneider-Thoma et al., 2022).

Antipsychotic polypharmacy is common in patients with schizophrenia, (Taipale et al., 2021) and how these therapies are associated with sleep outcomes is poorly known. In one study, using a higher number of antipsychotic medications was associated with less sleep problems. (Waters et al., 2012) In a small retrospective cohort study of clozapine polypharmacy, augmentation with risperidone increased sleep duration, while adding aripiprazole shortened sleep duration (Fernandez-Egea et al., 2021).

We have previously shown in this large, nationwide sample of patients with psychotic disorders, that the patients have more sleep problems, including both insomnia and hypersomnia symptoms, than the general population. (Cederlöf et al., 2022) In this study, we aim to explore how commonly used antipsychotics, namely clozapine, olanzapine, quetiapine, aripiprazole, and risperidone, are related to subjective sleep problems in patients with schizophrenia. We also aim to investigate how combinations of two antipsychotic medications and using no antipsychotic medications relate to sleep problems. We hypothesized that clozapine is strongly associated to long sleep duration and low rates of insomnia symptoms, and that aripiprazole will be associated with more insomnia symptoms.

2. Material and methods

2.1. Study sample

This study is a part of the SUPER research project, which examines psychotic disorders. The SUPER project is a part of the international Stanley Global Neuropsychiatric Genomics Initiative. In Finland, the Institute for Molecular Medicine Finland (FIMM), the Finnish Institute of Health and Welfare (THL) and the University of Helsinki oversaw the research project. The project was done in cooperation with all hospital districts in Finland.

2.2. SUPER and present study cohort

Patients with schizophrenia spectrum disorders (ICD-10 codes: F20–F29), bipolar disorder and psychotic depression (ICD-10 codes: F30.1, F30.2, F31, F32.3 and F33.3) were invited to participate through psychiatric in- and outpatient units, primary care, housing units and advertisements in local newspapers from the whole mainland of Finland. In the present study only patients with schizophrenia were included. The diagnoses were retrieved from the Finnish Care Register for Health Care (HILMO). The study has been approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa and by all participating healthcare organizations. Minors and individuals not able to give informed consent were not recruited into the study. Research nurses acquired written informed consent, after which the study protocol began. For further information about study protocol, and the interview and questionnaire data, see cohort profile article. (Lähteenvuo et al., 2023) Information about demographic variables is also included in the supplement.

The SUPER sample size was 10,411 patients. After excluding patients with no registry-based diagnosis or a diagnosis other than schizophrenia, there were 5752 patients left. After that we excluded patients over 80 years of age, and patients with no sleep or medication data, reaching the final sample size of 5466 patients. For our stepwise analyses (Supplementary Fig. A for STROBE Chart), we also studied patients with only one antipsychotic medication ($N = 1290$), and no other psychotropic medications, and patients with no other psychotropic medications than antipsychotic medications ($N = 2207$).

Psychotropic medications were defined by Anatomic Therapeutic Chemical classification (ATC) codes: antipsychotics (N05A, except for lithium), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A), and psycholeptics and psychoanaleptics in combination (N06C) (WHO, 2018). We included mood stabilizers in the psychotropic medications; namely carbamazepine (N03AF01), valproic acid (N03AG01), lamotrigine (N03AX09), and lithium (N05AN01) (Rapoport et al., 2009).

2.3. Questionnaire data (sleep)

From the questionnaire, subjective data on sleep was received. The full questions regarding sleep symptoms are included in the supplement. The questions were mainly based on population-based studies in Finland. (Aromaa and Koskinen, 2004; Heistaro, 2008; Koponen et al., 2018; Partinen and Gislason, 1995) The questions included total sleep duration (TSD), difficulty initiating sleep (DIS) (Heistaro, 2008), early morning awakenings (EMAs) (Heistaro, 2008), fatigue (FAT) (Aromaa, 2004), and sleep quality (SQ) (Partinen and Gislason, 1995). Long sleep duration (long SD) was defined as sleeping $\geq$10 h per day, (Diagnostic and Statistical Manual of Mental Disorders, 2013) and short sleep duration (short SD) as sleeping $\leq$6 h per day. Unreasonable responses on sleep duration (TSD $<$2 h or $\geq$ 18 h) were excluded ($N = 21$). DIS, EMAs,

and FAT were defined as having these problems often or nearly always. Poor sleep quality (poor SQ) was defined as having slept rather poorly or poorly during the last month.

2.4. Medication data

Medication data was retrieved from the interview of the patients. The question was:

What medications do you use regularly?

The names and dosages of the medicines were checked on the packaging, the prescription or on a printed medication list if the interviewee did not remember them. If no packaging or prescription was available, memory information was deemed sufficient. Injections were also recorded. Additionally, it was recorded if the medication was a regular medication or taken when needed, and whether it had been used during the last 7 days. For antipsychotics, we only included tablets and long-acting injectable medications that were taken regularly, and in the case of tablets, had been taken during the last 7 days. For the included antipsychotics, 2–4 % of patients did not have an available dose and were hence not included in the supplemental dose-related analyses.

We included the five most common antipsychotics in our analyses, meaning clozapine, olanzapine, quetiapine, aripiprazole, and risperidone. In our analyses of antipsychotic combinations, the threshold was 50 users, and thus all combinations of the five most used medications except for the combination of risperidone and aripiprazole ($N = 36$) were included.

2.5. Covariates

The covariates in all regression analyses were age and gender. We also conducted post-hoc analyses with additional covariates for the main analyses with the full study sample. These post-hoc covariates were analyzed separately, and included BMI, time of year as a four-split variable (December–February, March–May, June–August, September–November), *Z*-medications (benzodiazepine receptor agonists; zopiclone and zolpidem), sedative antidepressants (amitriptyline, doxepin, trazodone, trimipramine, mirtazapine, mianserin), (Wichniak et al., 2017), agomelatine, benzodiazepine medications (ATC codes N05BA, N05CD), time since first hospitalization due to psychosis, psychological distress, using the Mental Health Inventory-5 (MHI-5) (Berwick et al., 1991), hazardous alcohol use (Alcohol Use Disorders Identification Test-Concise) (Reinert and Allen, 2007; Alcohol abuse: Current Care Guidelines), and current smoking (last smoke today/yesterday). Further information on the assessments of alcohol and smoking are included in the supplement.

2.6. Statistical analysis

Firstly, we investigated the prevalence of antipsychotic and psychotropic medication use in the sample. We then conducted logistic regressions for the specific sleep problems, with gender and age as covariates. The first of our two main models included the full sample ($N = 5466$) and compared all patients using one antipsychotic medication to all patients not using that specific medication, thus allowing antipsychotic polypharmacy. The second model was head-to-head analyses between antipsychotic medications, and using no antipsychotic medication, and did not allow antipsychotic polypharmacy. The risk for sleep problems is reported using odds ratios (OR) with 95 % confidence intervals (CI).

When comparing frequencies of sleep problems according to medication status in the full sample, we included sleep problem frequencies in the general population, from the Health 2000 study. (Aromaa, 2004; Heistaro, 2008) In the Health 2000 study, 7167 Finnish persons aged 18–80 years old answered largely the same sleep-related questions as in SUPER. Poor SQ was assessed only in the SUPER questionnaire. The sleep data from Health 2000 has been used by our study group previously to compare sleep in the SUPER sample to the general population. (Cederlöf et al., 2022).

In supplemental analyses, we conducted stepwise analyses in smaller samples, firstly including patients with 0–1 antipsychotic medications, and no other psychotropic medications ($N = 1276$), and secondly also patients with multiple antipsychotics, but no other psychotropic medications ($N = 2109$). As the results were similar (Supplementary Table A–B) as in the full sample analysis, we used the most real-world representative model with all schizophrenia patients included. To analyze antipsychotic polypharmacy's relation to sleep problems, we conducted logistic regression models and compared antipsychotic combinations to the use of either antipsychotic within those combinations individually. We also split olanzapine, aripiprazole, and risperidone, and compared long-acting injectable prescriptions with tablet prescriptions. Finally, for quetiapine, we compared medium/high versus low-dose prescriptions, with ≤100 mg being categorized as low-dose quetiapine (Schizophrenia: Current Care Guidelines, 2022).

Holm-Bonferroni corrections controlled the family-wise error rates in all analyses, with each sleep problem considered a family. For example, $p = .05/6$ (number of medication groups) =0.0083 was the lowest significance threshold in the full sample analyses. (Holm, 1979).

3. Results

3.1. Demographics

Demographic information retrieved from the interview of the patients is in Table 1. Mean age was 48.3 years. Mean time since first hospitalization due to psychosis was 21.9 years, and for <2 % this time was under 1 year. 59.1 % of the patients lived independently.

3.2. Prevalence of antipsychotic use

Medication data is in Table 2. Clozapine was the most frequently used antipsychotic medication, followed by olanzapine, quetiapine, aripiprazole, and risperidone, respectively. 2.9 % of patients used no antipsychotic, 51.3 % used one antipsychotic, 37.8 % used 2 antipsychotics, and 8.0 % 3 or more antipsychotic medications. Of the 2.9 % patients using no antipsychotic, 54.7 % used some psychotropic medication, compared to 60.3 % of patients with antipsychotic medications that also used some other psychotropic medication.

3.3. Sleep problems and antipsychotic use

3.3.1. Analyses including full sample

Sleep problem frequencies related to the included antipsychotic medications are in Fig. 1, and regression results in Table 3. Clozapine

Table 1
Demographics and baseline sleep problem prevalence for study sample ($N = 5466$).

Age, M (SD)	48.3 years (13.9)
Gender, % male	57.4 %
Living independently	59.1 %
Time since first psychotic episode, M (SD)	21.9 years (12.7)
Basic education	40.0 %
Upper secondary education	43.7 %
Higher education	16.3 %
BMI, M (SD)	30.5 (6.89)
MHI-5, M (SD)	65.5 (19.5)
Difficulties initiating sleep	25.1 %
Early morning awakenings	35.3 %
Fatigue	41.2 %
Poor sleep quality	10.8 %
Short sleep duration	8.1 %
Long sleep duration	37.7 %

Abbreviations: BMI = body mass index, MHI-5 = Mental Health Inventory-5.

Table 2
Description of medication use in sample by age and sex. For antipsychotic medications only regular medications are included, while for the other medications also prescriptions for taken when needed were included.

	18–40 M (*N* = 1056)	18–40 W (*N* = 652)	41–60 M (*N* = 1436)	41–60 W (*N* = 1095)	61–80 M (*N* = 649)	61–80 W (*N* = 578)
Clozapine (*N* = 2175)	45.8 %	47.1 %	45.4 %	40.5 %	28.0 %	18.5 %
CZP monotherapy (*N* = 1192)	24.5 %	23.9 %	24.1 %	20.7 %	16.3 %	9.5 %
Olanzapine (*N* = 1657)	30.3 %	20.9 %	31.0 %	27.5 %	38.7 %	35.3 %
OLZ monotherapy (*N* = 711)	13.5 %	8.0 %	12.5 %	12.0 %	16.6 %	17.0 %
Quetiapine (*N* = 1208)	17.0 %	24.5 %	19.8 %	26.0 %	20.8 %	28.2 %
QTP monotherapy (*N* = 223)	2.9 %	5.1 %	2.8 %	4.7 %	4.9 %	6.2 %
Aripiprazole (*N* = 1000)	25.6 %	29.1 %	15.5 %	16.7 %	8.6 %	13.7 %
ARP monotherapy (*N* = 206)	5.6 %	8.4 %	2.2 %	3.3 %	0.5 %	3.6 %
Risperidone (*N* = 662)	8.0 %	7.1 %	13.0 %	11.3 %	17.1 %	18.9 %
RIP monotherapy (*N* = 216)	3.7 %	2.1 %	4.2 %	3.6 %	4.8 %	5.7 %
Mean of antipsychotics (APs), (SD)	1.47 (0.65)	1.49 (0.69)	1.55 (0.72)	1.53 (0.72)	1.51 (0.73)	1.53 (0.72)
1 AP medication (*N* = 2804)	55.7 %	53.1 %	50.3 %	49.4 %	50.1 %	48.6 %
2 AP medications (*N* = 2065)	36.6 %	36.5 %	38.8 %	38.4 %	36.5 %	39.1 %
≥3 AP medications (*N* = 438)	5.9 %	7.5 %	8.6 %	8.6 %	9.4 %	8.5 %
No AP medications (N = 159)	1.8 %	2.9 %	2.3 %	3.7 %	4.0 %	3.8 %
Benzodiazepines (*N* = 1678)	22.0 %	24.5 %	31.0 %	35.8 %	35.8 %	39.9 %
Mood stabilizers[a] [and] [b] (*N* = 681)	12.5 %	15.8 %	11.7 %	13.8 %	9.7 %	11.1 %
Sedative antidepressant[b] (*N* = 467)	7.2 %	7.0 %	8.9 %	7.1 %	13.3 %	9.6 %
Z-medication[c] (*N* = 219)	2.2 %	2.1 %	3.6 %	5.5 %	4.6 %	6.9 %

Abbreviations: M = men, W = women, AP = antipsychotic, CZP = Clozapine, OLZ = Olanzapine, QTP = Quetiapine, ARP = Aripiprazole, RIP = Risperidone.
[a] Lithium, carbamazepine, valproic acid, lamotrigine
[b] Amitriptyline, doxepin, trazodone, trimipramine, mirtazapine, mianserin
[c] Benzodiazepine receptor agonists (zolpidem, zopiclone)

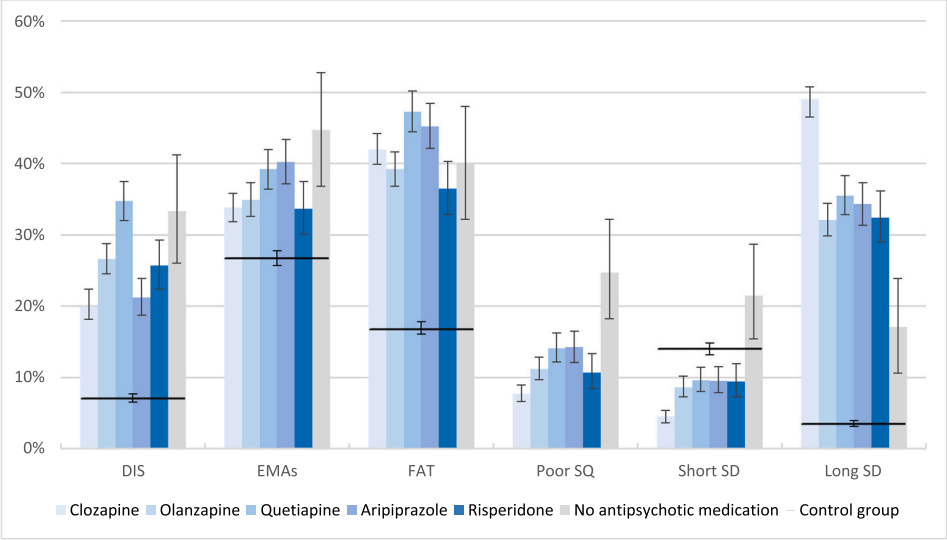

Fig. 1. Sleep problems in the whole sample according to the most common antipsychotic medications, and to no antipsychotic medication. The control group is Health 2000, a Finnish population representative sample. 95 % confidence intervals are included. Abbreviations: DIS = Difficulties initiating sleep, EMAs = early morning awakenings, FAT = fatigue, Poor SQ = poor sleep quality, Short SD = short sleep duration, Long SD = long sleep duration.

users had a very high prevalence of long SD (49.0 % of patients using clozapine, and in regression analyses compared to patients not using clozapine, OR = 2.05, CI = 1.83–2.30, $p < .001$). Clozapine use was also associated with less DIS, poor SQ, and short SD. Aripiprazole use was associated with more EMAs, poor SQ (14.2 %, OR 1.49, CI = 1.21–1.84), short SD, and less long SD. Quetiapine was associated with more DIS (34.7 %, OR = 1.82, CI = 1.58–2.09, $p < .001$), EMAs, FAT, and poor SQ. Olanzapine was associated with less long SD. Risperidone had no significant associations with sleep. Using no antipsychotic medication was strongly associated with low rates of long SD and high rates of short SD (21.5 %, OR = 2.97, CI = 1.98–4.44, p < .001), as well as frequent poor SQ.

In Fig. 1, a control group sample of the general Finnish population was included. Compared to the general population, regardless of medication status, patients with schizophrenia had more DIS, EMAs, FAT, and long SD. Regarding short SD, only patients with no antipsychotic medication had a higher prevalence than the general population.

3.3.2. *Head-to-head analyses*

Results from head-to-head analyses are in Fig. 2. Only patients with individual antipsychotic use were included.

Clozapine was associated with more long SD compared to using any other antipsychotic medication, and consistently associated with less insomnia symptoms and less short SD compared to using quetiapine, aripiprazole, or using no antipsychotic medication. Similarly, olanzapine was associated to less sleep problems compared to patients using quetiapine, aripiprazole or using no antipsychotic medication (i.e., olanzapine vs. aripiprazole for EMAs OR = 0.41, CI = 0.29–0.58, $p <$ .001). The only significant association in the head-to-head analyses between clozapine and olanzapine was clozapine being associated with

Table 3
Results from multivariate logistic regression analyses with difficulties initiating sleep, early morning awakenings, fatigue, sleep quality, long and short sleep duration. The reference groups were all patients not using the specific medication. Patients with antipsychotic polypharmacy were included in the analyses. Covariates were gender and age. Results significant after Holm-Bonferroni correction are bolded.

	N (%)	OR	CI	p	N (%)	OR	CI	p	N (%)	OR	CI	p
	Difficulties initiating sleep				Early morning awakenings				Fatigue			
Clozapine	431 (19.9 %)	**0.65**	**0.57–0.74**	**<0.001**	732 (33.9 %)	0.96	0.85–1.07	0.448	910 (42.0 %)	0.99	0.88–1.11	0.872
Olanzapine	440 (26.6 %)	1.11	0.97–1.26	0.154	577 (34.9 %)	0.96	0.85–1.09	0.513	648 (39.2 %)	0.94	0.85–1.06	0.346
Quetiapine	416 (34.7 %)	**1.82**	**1.58–2.09**	**<0.001**	472 (39.2 %)	**1.20**	**1.05–1.38**	**0.006**	570 (47.3 %)	**1.36**	**1.19–1.55**	**<0.001**
Aripiprazole	211 (21.2 %)	0.81	0.68–0.96	0.014	401 (40.2 %)	**1.39**	**1.20–1.60**	**<0.001**	451 (45.2 %)	1.09	0.95–1.26	0.223
Risperidone	169 (25.7 %)	0.99	0.82–1.19	0.891	222 (33.7 %)	0.87	0.74–1.04	0.131	241 (36.5 %)	0.87	0.73–1.03	0.100
No AP medication	53 (33.3 %)	1.45	1.04–2.03	0.025	71 (44.7 %)	1.42	1.03–1.96	0.030	63 (39.9 %)	0.97	0.70–1.35	0.862

	N (%)	OR	CI	p	N (%)	OR	CI	p	N (%)	OR	CI	p
	Poor sleep quality				Short sleep duration				Long sleep duration			
Clozapine	167 (7.7 %)	**0.57**	**0.47–0.69**	**<0.001**	97 (4.5 %)	**0.48**	**0.38–0.61**	**<0.001**	1058 (49.0 %)	**2.05**	**1.83–2.30**	**<0.001**
Olanzapine	184 (11.2 %)	1.06	0.88–1.28	0.527	141 (8.6 %)	0.97	0.78–1.20	0.775	530 (32.1 %)	**0.75**	**0.67–0.85**	**<0.001**
Quetiapine	170 (14.1 %)	**1.46**	**1.21–1.77**	**<0.001**	114 (9.6 %)	1.25	0.99–1.57	0.058	423 (35.5 %)	0.89	0.78–1.03	0.111
Aripiprazole	141 (14.2 %)	**1.49**	**1.21–1.84**	**<0.001**	94 (9.5 %)	**1.64**	**1.28–2.10**	**<0.001**	340 (34.3 %)	**0.69**	**0.60–0.80**	**<0.001**
Risperidone	70 (10.7 %)	0.97	0.75–1.27	0.842	62 (9.4 %)	1.01	0.76–1.34	0.776	213 (32.4 %)	0.87	0.73–1.04	0.127
No AP medication	39 (24.7 %)	**2.76**	**1.90–4.01**	**<0.001**	34 (21.5 %)	**2.97**	**1.98–4.44**	**<0.001**	27 (17.1 %)	**0.35**	**0.23–0.53**	**<0.001**

Abbreviations: AP = antipsychotic.

more long SD. Risperidone was associated with less sleep problems, particularly less FAT, but less consistently than olanzapine and clozapine (i.e., quetiapine vs risperidone for FAT, OR = 1.82, C = 1.22–2.70, p < .001).

Quetiapine was associated with more DIS compared to all other antipsychotics, and the only antipsychotic not associated with less DIS compared to patients using no antipsychotic. Aripiprazole was associated with more EMAs compared to using clozapine, olanzapine or quetiapine, and the only antipsychotic not associated with less poor SQ, and short SD compared to using no antipsychotic.

Using no antipsychotic medication was strongly associated with having more sleep problems, including DIS, EMAs, poor SQ, and short SD, and with less long SD compared to using clozapine, olanzapine, quetiapine, or risperidone.

3.3.3. Supplemental analyses

We analyzed how sleep problems related to antipsychotic combinations therapies compared to sole antipsychotic use. Generally, combinations of antipsychotics were associated with more sleep problems compared to using only either of the antipsychotics. Combinations with aripiprazole were associated with more EMAs than using the counterpart (clozapine or quetiapine) in those combinations individually. However, conversely, these combinations were not associated with ***fewer*** EMAs compared to using aripiprazole individually. However, the combination of clozapine and aripiprazole was associated with less long SD than using solely clozapine.

We found no significant difference in relation to sleep problems for long-acting injectable medications (LAIs) for olanzapine, risperidone, and aripiprazole, versus the oral form of the medication (Supplementary Table D). Low- and medium/high-dose quetiapine were both associated with DIS, FAT, and poor SQ, with no significant differences found. (Supplementary Table E).

Regarding post-hoc analyses, the associations that significantly changed were between quetiapine and EMAs, which was lost when considering hazardous alcohol use, smoking, *Z*-medications, benzodiazepines, BMI, time of year, or psychological distress, and between quetiapine and poor SQ, for which psychological distress changed the result significantly (Supplementary Table G).

4. Discussion

4.1. General results

In this study, we showed in a large sample of patients with schizophrenia that the prevalence of sleep problems is strongly related to the antipsychotic medications the patients use, both in head-to-head analyses between different antipsychotics and in full-sample analyses with antipsychotic polypharmacy. By including patients using no antipsychotic medication, and by comparing the prevalence of sleep problems to a large sample of the general population, the findings in this study brings comprehensive insight on subjective sleep problems in schizophrenia.

Previously, clozapine and olanzapine have been found to consistently increasing sleep. (Monti et al., 2017; Wilson et al., 2019) Our findings support this view. Clozapine was strongly associated with long SD compared to all other antipsychotics and to low rates of insomnia symptoms. Olanzapine was in head-to-head analyses, which were not impacted by the frequent clozapine use, similarly associated with less insomnia symptoms.

Quetiapine is widely used as a hypnotic medication but has had mixed results in sleep studies in patients with schizophrenia. (Monti et al., 2017; Wilson et al., 2019) Quetiapine was here associated with more insomnia symptoms, with DIS more frequent than for any other antipsychotic. Previously, some studies in patients with schizophrenia using quetiapine have reported high adverse effect rates of insomnia, (Miller et al., 2023; Miller and McCall, 2022) and increased sleep latency was found in an objective study, (Monti et al., 2017) while increased daytime fatigue was found in one study for quetiapine compared to lurasidone and placebo. (Loebel et al., 2014) The findings in our and previous studies underline the need for more research on quetiapine's effect on sleep in schizophrenia. Aripiprazole's impact on sleep has not been extensively studied. In adverse effect studies there have been high rates of insomnia complaints, and low rates of hypersomnia complaints. (Krystal et al., 2008; Stip and Tourjman, 2010) Here, it was associated with more sleep problems and the only medication to not be associated with less poor SQ and short SD compared to using no antipsychotic medication, indicating a clear difference in its relation to sleep compared to other antipsychotics. This underlines the necessity of evaluating insomnia symptoms in patients using aripiprazole.

Patients with no antipsychotic medication had, compared to patients using antipsychotics, high rates of poor sleep quality and short SD, and a

Difficulties initiating sleep					
CZP	0.77 (0.61-0.98)	0.40 (0.29-0.54)	1.16 (0.77-1.74)	1.00 (0.69-1.47)	0.45 (0.31-0.65)
1.10 (0.89-1.37)	**OLZ**	0.52 (0.38-0.73)	1.47 (0.96-2.25)	1.29 (0.88-1.90)	0.59 (0.41-0.86)
1.03 (0.75-1.42)	0.93 (0.67-1.30)	**QTP**	2.91 (1.80-4.72)	2.44 (1.56-3.80)	1.11 (0.72-1.71)
0.55 (0.40-0.75)	0.41 (0.29-0.58)	0.52 (0.34-0.79)	**ARP**	0.93 (0.54-1.61)	0.39 (0.23-0.67)
0.75 (0.55-1.03)	0.70 (0.51-0.98)	0.76 (0.51-1.14)	1.76 (1.14-2.72)	**RIP**	0.47 (0.29-0.75)
0.55 (0.39-0.78)	0.50 (0.35-0.71)	0.53 (0.34-0.81)	1.14 (0.73-1.80)	0.70 (0.46-1.06)	**NO**
Early morning awakenings					
Fatigue					
CZP	1.22 (1.00-1.49)	0.84 (0.62-1.13)	0.73 (0.54-0.99)	1.45 (1.06-1.99)	1.03 (0.72-1.46)
0.72 (0.50-1.03)	**OLZ**	0.65 (0.47-0.89)	0.61 (0.44-0.85)	1.15 (0.83-1.61)	0.79 (0.55-1.13)
0.49 (0.30-0.79)	0.68 (0.42-1.11)	**QTP**	0.92 (0.61-1.38)	1.82 (1.22-2.70)	1.22 (0.80-1.86)
0.32 (0.20-0.50)	0.42 (0.26-0.68)	0.71 (0.40-1.26)	**ARP**	2.09 (1.37-3.19)	1.33 (0.85-2.09)
0.61 (0.36-1.02)	0.83 (0.50-1.39)	1.16 (0.63-2.12)	2.02 (1.08-3.77)	**RIP**	0.67 (0.44-1.04)
0.20 (0.13-0.31)	0.28 (0.18-0.45)	0.39 (0.22-0.68)	0.56 (0.33-0.98)	0.35 (0.19-0.62)	**NO**
Poor sleep quality					
Short sleep duration					
CZP	0.68 (0.44-1.06)	0.49 (0.27-0.88)	0.18 (0.11-0.31)	0.46 (0.26-0.81)	0.16 (0.10-0.26)
2.26 (1.85-2.76)	**OLZ**	0.72 (0.41-1.27)	0.25 (0.14-0.44)	0.66 (0.38-1.13)	0.26 (0.16-0.42)
2.21 (1.61-3.03)	0.95 (0.68-1.33)	**QTP**	0.42 (0.22-0.82)	0.89 (0.46-1.72)	0.35 (0.19-0.64)
2.89 (2.08-4.02)	1.39 (0.97-2.00)	1.35 (0.87-2.10)	**ARP**	2.62 (1.32-5.18)	0.73 (0.40-1.31)
3.03 (2.16-4.23)	1.31 (0.92-1.87)	1.34 (0.87-2.06)	0.97 (0.61-1.55)	**RIP**	0.41 (0.23-0.73)
4.89 (3.16-7.57)	2.13 (1.35-3.36)	2.22 (1.33-3.69)	1.51 (0.87-2.60)	1.71 (1.00-2.91)	**NO**
Long sleep duration					

Fig. 2. Results from head-to-head logistic regression analyses for the antipsychotic medications and using no antipsychotic medication. Only sole users of each antipsychotic medication were included. Age and gender were included as covariates. Significant results after Holm-Bonferroni correction are colored.

comparatively lower prevalence of long SD, consistent with polysomnographic studies of patients with schizophrenia without antipsychotic use. (Chan et al., 2017; Monti et al., 2017).

When comparing sleep problem prevalence to the general population, the findings illuminated how both schizophrenia and antipsychotic medications are related to sleep problems. Patients with schizophrenia had regardless of antipsychotic medication status more insomnia symptoms, consistent with previous studies showing the persistence of insomnia symptoms in schizophrenia. (Freeman et al., 2019) Only patients using no antipsychotics had a higher prevalence of short SD than the general population. Still, also long SD had a clearly higher prevalence for patients using no antipsychotics than in the general population, indicating that sleep duration in schizophrenia is not merely related to antipsychotic medications. This finding is interesting in the context of a polygenic risk score study finding a bidirectionally causal genetic relationship between schizophrenia and sleep duration. (Dashti et al., 2019).

Sedation is a common side effect related to antipsychotic use that may decrease quality of life and medication compliance in patients using antipsychotics, thus leading to worse health outcomes. (Doane et al., 2020; Stahl et al., 2021; Tandon et al., 2020) As under 2 % of the

patients had under 1 year since their first psychosis, the high sedation rate is unlikely to be intermittent during antipsychotic initiation and could instead be a problem for many patients in this sample, supported by previous findings of persistent sedation associated with particularly clozapine, but also other antipsychotics. (Huhn et al., 2019; Schneider-Thoma et al., 2022) However, insomnia symptoms are strongly associated with worse outcomes including psychotic symptoms, (Waite et al., 2020) underlining the need for sleep-supporting medications and the delicate balance between using more and less sedating antipsychotics. (Krystal et al., 2008).

As there are a multitude of neurotransmitters impacting sleep and wakefulness, and antipsychotics have affinity to a multitude of neurotransmitter receptors, the mechanisms of antipsychotic-related sleep impacts, are not entirely clear. (Fang et al., 2016) That clozapine use was strongly associated to long SD could be explained by high affinities to histaminergic H1-receptors, noradrenergic α1-receptors, and muscarinic cholinergic M1-receptors (Fang et al., 2016; Monti et al., 2017). Regarding H1-receptors, clozapine has a stronger affinity than any other antipsychotic, and H1-receptor gene variants have been shown to affect the level of sedation associated to clozapine, (Fang et al., 2016; Solismaa et al., 2017) showing the potential for utilizing pharmacogenetics in avoiding side-effects such as sedation related to antipsychotic use. (Arranz et al., 2021).

Antipsychotic combinations were generally more associated with sleep problems than using either antipsychotic on their own, in opposition to a study showing that using more antipsychotics was associated with less sleep problems. (Waters et al., 2012) However, combining aripiprazole and clozapine seemed to somewhat mitigate the long SD association of clozapine use, consistent with a previous study (Fernandez-Egea et al., 2021).

4.2. Strengths and limitations

One of the main strengths of this study is the large, nationwide sample of patients with schizophrenia, which enabled extensive analyses comparing different medications. The sleep outcomes were clearly defined and systematically measured in the whole sample. The vast information regarding all patients enabled thorough post-hoc analyses for confounding factors, such as BMI, psychological distress, and alcohol. This study of real-world data does not have the same limitations of underreporting as adverse effect studies may have. (Cascade et al., 2010; Loke et al., 2011).

The 5466 study participants were from the whole mainland of Finland. When compared to national register-based data of antipsychotic use in patients with schizophrenia in Finland, (Taipale et al., 2021) our sample had more clozapine use and antipsychotic polypharmacy, and fewer patients used no antipsychotics. These differences are probably due to the nature of the sample, as many patients were recruited from healthcare settings and residential facilities. Additionally, the mean time since onset was quite high, 21.9 years. Still, clozapine has the highest world-wide use in Finland, (Bachmann et al., 2017) and is the second-most used antipsychotic, prescribed to 22 % of patients with schizophrenia. (Taipale et al., 2021).

Regarding limitations, the cross-sectional nature of the study makes it impossible to draw conclusions about causality regarding the relationship between sleep problems and antipsychotic medications. The association between quetiapine and DIS, but also other associations, as those for antipsychotic combinations, must be seen in this context. Quetiapine is broadly used for patients with insomnia symptoms, (Wine et al., 2009) and may hence have been prescribed to patients with sleep problems. However, associations between quetiapine and insomnia symptoms were significant regardless of dosage or whether it was used as the sole antipsychotic or not.

Only subjective sleep was analyzed in this study. There is a discrepancy between subjective and objective sleep, (Baker et al., 1999) also in patients with schizophrenia. (Chung et al., 2020) Still, sleep problems are in clinical work mainly based on subjective complaints, which are strongly related to quality of life. (Ritsner et al., 2004) Hence, it is valuable for better understanding the patient experience of sleep problems related to antipsychotic use. The sleep questionnaire was based on Finnish population-based studies. This enabled comparisons with the general population, a strength, but the sleep questionnaire has not been validated, which is a limitation. As limitations of the medication data, it was self-reported, and we had no data on usage duration. Self-report has previously been found to be adequately reliable for Finnish patients with antipsychotic medications. (Haukka et al., 2007) Regarding confounding factors, we were not able to assess psychotic symptoms. Considering there is a bidirectional relationship between insomnia and psychotic symptoms, (Waite et al., 2020) it would in future studies be valuable to assess psychotic symptoms and investigate possible interactions between antipsychotic effectiveness and insomnia symptoms. Finally, no non-psychotropic medications were included - even though they may impact sleep (Novak and Shapiro, 1997) - as these were considered outside the scope of this article.

As this is an observational study, no treatment recommendations can be based on the findings here. The first-line treatment of insomnia is regardless of comorbidities cognitive-behavioral therapy for insomnia (CBT—I), according to the European Insomnia Guideline. (Riemann et al., 2023) Our findings support the need for future prospective studies for a better understanding of the relationship between different antipsychotic medications and sleep.

5. Conclusions

Sleep problem prevalence is strongly related to the antipsychotic treatment the patients use. Clozapine and olanzapine are associated with less insomnia symptoms. Clozapine is also associated to a markedly long sleep duration. Aripiprazole and quetiapine are associated with more insomnia symptoms. Antipsychotic medication use is generally associated with having less sleep problems, except for long sleep duration. This study underlines both the necessity of evaluating the antipsychotic treatment when treating sleep problems in schizophrenia, and of assessing the prevalence of sleep problems in patients with antipsychotic treatment.

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The funding organizations had no role in the design or execution of the study; in the collection, management, analysis, or interpretation of data; in the preparation, review, or approval of the manuscript; or in the decision to submit the manuscript for publication.

CRediT authorship contribution statement

Erik Cederlöf: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Conceptualization. **Minna Holm:** Writing – review & editing, Writing – original draft, Supervision, Methodology. **Heidi Taipale:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Jari Tiihonen:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Antti Tanskanen:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Markku Lähteenvuo:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Data curation. **Kaisla Lahdensuo:** Writing – review & editing, Writing – original draft, Project administration. **Olli Kampman:** Writing – review & editing, Writing – original draft, Project administration. **Asko Wegelius:** Writing – review & editing, Writing – original draft, Project administration. **Erkki Isometsä:** Writing – review & editing, Writing – original draft. **Tuula Kieseppä:** Writing – review & editing, Writing – original draft, Project administration. **Aarno Palotie:** Writing – review & editing, Writing – original draft, Project administration, Data curation. **Jaana Suvisaari:** Writing – review & editing,

Writing – original draft, Project administration, Methodology. **Tiina Paunio:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Asko Wegelius:** Writing – review & editing, Writing – original draft, Project administration.

Declaration of competing interest

Regarding conflicts of interest, Markku Lähteenvuo is an owner and board member of Genomi Solutions Ltd. and Nursie Health Ltd. and has received honoraria from Sunovion, Orion Pharma, Janssen-Cilag, Otsuka Pharma, Lundbeck, and Medscape, travel funds from Sunovion, and research grants from the Finnish Medical Foundation, the Emil Aaltonen Foundation, and the Finnish Cultural Foundation. Jari Tiihonen has participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution; has received personal fees from the Finnish Medicines Agency (Fimea), European Medicines Agency (EMA), Eli Lilly, Janssen-Cilag, Lundbeck, and Otsuka; is a member of the advisory board for Lundbeck; and has received grants from the Stanley Foundation and the Sigrid Jusélius Foundation. None of the other authors report any financial relationships with commercial interests.

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Appendix A. Supplementary data

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