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Association of antidepressant and benzodiazepine use, and anticholinergic burden with cognitive performance in schizophrenia

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ABSTRACT

Schizophrenia is characterized by cognitive impairment affecting everyday functioning. Earlier research has hypothesized that antidepressants may associate with better cognitive functioning, but results are mixed. This study explored the association between antidepressant use and cognitive performance in terms of reaction time and visual learning in a clinical sample. In addition, we examined benzodiazepine use and anticholinergic burden. Study participants were drawn from the SUPER-Finland cohort, collected among patients with psychotic illnesses in 2016–2018 throughout Finland (n = 10,410). The analysis included adults with a schizophrenia diagnosis (F20) and results from a cognitive assessment (n = 3365). Information about medications and psychosocial factors were gathered through questionnaire and interview. Cognitive performance was assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB) with two subtests measuring reaction time and visual learning. Almost 36 % of participants used at least one antidepressant. The use of antidepressants in general was not associated with performance in the reaction time and visual learning tasks. However, the use of SNRI antidepressants was associated with a faster reaction time. Benzodiazepine use and a higher anticholinergic burden were associated with poorer performance in both tests. The results strengthen earlier findings that there is no association between antidepressant use in general and cognitive performance in schizophrenia. However, the association of SNRI medications with a faster reaction time warrants further research. Moreover, the results suggest that more attention should be paid to the anticholinergic burden of the medications used by patients with schizophrenia, as well as avoiding continuous benzodiazepine use.

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1. Introduction

Schizophrenia belongs to one of the most burdening health problems in the world (James et al., 2017). Extensive evidence demonstrates that cognitive deficits are among its core symptoms (Fioravanti et al., 2012; Sheffield et al., 2018; Velthorst et al., 2021). Neurocognitive functioning in patients with schizophrenia is related to functional outcomes important for daily life (Fett et al., 2011; Fu et al., 2017). Cognitive impairment is typically generalized throughout cognitive functions. The cognitive domains especially affected include memory and learning, working memory, executive function, attention, and information processing speed (Reichenberg, 2010; Fioravanti et al., 2012). It has been suggested that the deficit in information processing speed may be at the core of the cognitive impairment (Dickinson et al., 2007; Thuaire et al., 2020). Finding ways of reducing the cognitive burden of schizophrenia is an important ongoing effort.

Since depression is frequent among patients with schizophrenia (Buckley et al., 2008), prescribing antidepressants is commonplace in clinical practice (Mao and Zhang, 2015). It has been suggested that, in addition to treating depressive symptoms, augmenting antipsychotic medication with antidepressants may result in better cognitive functioning. Empirical evidence is mixed. Meta-analyses suggest that while antidepressants may have small beneficial effects on depressive and negative symptoms (Helfer et al., 2016), antidepressant use in general has no significant effects on cognitive performance (Vernon et al., 2014). Nevertheless, individual randomized controlled trials suggest that mirtazapine (Stenberg et al., 2010, 2011; Cho et al., 2011; Delle Chiaie et al., 2017) and mianserin (Poyurovsky et al., 2003) may have small favorable effects. One naturalistic study demonstrated that the use of venlafaxine was associated with better verbal memory (Steen et al., 2015). These findings are contrasted with trials that found no significant effects of mirtazapine (Berk et al., 2009), citalopram (Friedman et al., 2005; Dawes et al., 2012), fluvoxamine (Niitsu et al., 2012), and duloxetine (Micó et al., 2011) on cognitive performance. In a Finnish cohort, cumulative lifetime use of antidepressants was not associated with cognitive performance in schizophrenia (Hulkko et al., 2017).

Benzodiazepines are often prescribed for patients with schizophrenia, for example, to treat comorbid anxiety or alleviate the side-effects of neuroleptics (Paton et al., 2000). There is mounting evidence from various patient groups that long-term benzodiazepine use may impair cognitive performance (Crowe and Stranks, 2018). Several studies suggest that long-term benzodiazepine use is associated with lower cognitive functioning also in psychosis spectrum disorders (Savić et al., 2021) including schizophrenia (Baandrup et al., 2017; Fond et al., 2018). Benzodiazepine use has even been linked with increased mortality risk in schizophrenia (Fontanella et al., 2016; Tiihonen et al., 2016).

Patients with schizophrenia often use concurrently several psychotropic medications, including antipsychotics, that have significant anticholinergic properties (Joshi et al., 2021). It has been demonstrated that a higher anticholinergic burden of medications may be associated with lower cognitive performance (Minzenberg et al., 2004; Joshi et al., 2021; Haddad et al., 2023). Increases in anticholinergic load has been found to be associated with lower composite cognitive functioning or a decline in individual cognitive domains, specifically learning and memory, processing speed, attention, and executive function (Georgiou et al., 2021).

The main aim of this study was to investigate the association between antidepressant use and cognitive performance measured with reaction time and visual learning in patients with schizophrenia. In addition, we investigated the association of benzodiazepine use and anticholinergic medication burden with performance on the two cognitive tests. Based on earlier research, we hypothesized that antidepressant use in general would not be associated with cognitive performance, but mirtazapine use would be associated with slightly better cognitive performance. Furthermore, we anticipated that benzodiazepine use, and higher anticholinergic burden would be associated with poorer performance on the cognitive tasks.

2. Materials and methods

2.1. Study participants

The study participants were derived from the SUPER-Finland patient cohort (www.superfinland.fi). The cohort was collected as part of the international Stanley Global Neuropsychiatric Genetics Initiative. The cohort consists of 10,410 participants with a history of at least one psychotic episode. The data in the cohort were collected during three years between 2016 and 2018. The Coordinating Ethical Committee of the Helsinki and Uusimaa Hospital Region approved the SUPER Study (Reference number 202/13/03/00/15). All participants signed an informed consent that permits the use of collected samples and data for the original study of psychiatric disorders. A more detailed SUPER study protocol has been published in a separate article (Lähteenvuo et al., 2023).

The SUPER cohort includes participants with a history of at least one clinically diagnosed episode of psychotic illness, and they have been recruited throughout Finland. The participants had schizophrenia (ICD-10 F20, 58 % of the participants), bipolar disorder (F30, F31, 16 %), schizoaffective disorder (F25, 10 %), psychotic depression (F32.3, F33.3, 5 %), or other ICD-10 psychotic disorders (11 %). Participants were recruited from in- or outpatient psychiatric care, primary care units, and supported housing units. The data contain a wide array of information of the participants consisting of psychosocial and medical information gathered through an interview and a questionnaire, a short cognitive assessment, blood samples or saliva sample for DNA extraction, and longitudinal data from several nationwide registers. The cohort represents the most comprehensive clinical dataset of Finnish persons with psychotic disorders to date, with a wide geographical distribution.

For this study, 5752 participants diagnosed with schizophrenia (ICD-10 F20) were chosen from the SUPER cohort. Diagnostic information was derived from the Finnish National Care Register for Health Care. The study population was further limited to working-age persons (ages 18–70). Participants who received their schizophrenia diagnosis before the age of 13 (very early-onset) were excluded. Moreover, only those participants who had full information about medication and complete results from the cognitive assessments were included. This procedure resulted in a final study population of 3365 participants in total (see Fig. 1).

The study participants took part in a baseline study assessment consisting of filling out a questionnaire and an interview, including a brief cognitive assessment. The average length of one study assessment was 60 to 90 min. The data collection was carried out by research nurses who had been trained for the data collection procedures by expert clinicians.

2.2. Medication variables

All medications used regularly by the participant were listed. The information about medicines was self-reported, but if the participant could not remember their medicines, they were checked from medicine containers or prescriptions. For each medication, participants were asked whether they had used it within the past 7 days. Only medications used within this timeframe were included in the analysis. For the analysis, medicines were transformed to ATC codes used to create grouping variables: different antidepressant types (ATC codes starting with N06), benzodiazepines (ATC codes starting with N05BA, N05CD, and N03AE), and antipsychotics (ATC codes starting with N05A). Antidepressants were organized into five categories: selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNRI), mirtazapine, tricyclic antidepressants (TCA), and other.

Anticholinergic burden was calculated using a modified

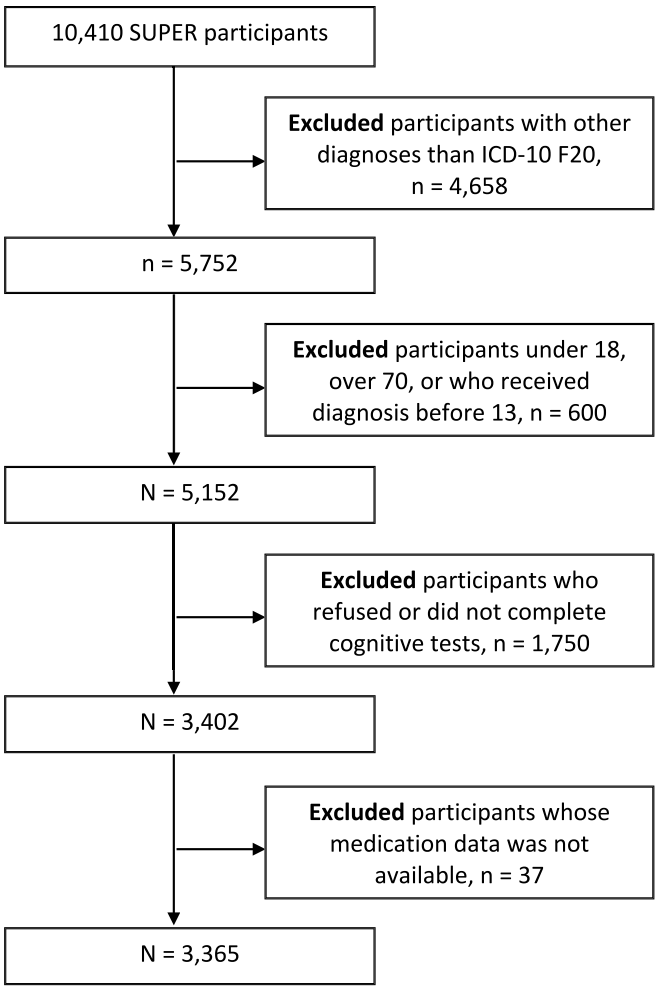

Fig. 1. Exclusion criteria for this study.

Anticholinergic Burden Scale (ACB) (Joshi et al., 2021). ACB is a validated expert rating scale for the anticholinergic burden of medications. It has good clinical validity over other measures of anticholinergic load (Hsu et al., 2017). The scale was used by assigning a rating for each medication based on its anticholinergic properties: 1 for low, 2 for moderate, and 3 for strong. These ratings were derived from earlier research (Boustani et al., 2008; Joshi et al., 2021). These points for each participant were then summed, yielding the total anticholinergic burden score of their medication. The number of antipsychotics used by each participant was computed into one variable.

2.3. Cognitive assessment

During the interview, the participants performed two tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) with a tablet computer. Psychologists had trained the nurses administering CANTAB for the task. CANTAB has been extensively used in studies assessing cognitive performance in schizophrenia (Rodriguez-Toscano et al., 2020). It has been found to produce similar results to those obtained with traditional neuropsychological tests, especially in visuospatial deficits (Levaux et al., 2007). Two subtests measuring information processing speed (RTI) and visual learning and memory (PAL) were chosen since these subtests reflect the central cognitive deficits in schizophrenia (Fioravanti et al., 2012). Especially information processing speed may be at the core of the cognitive deficits in schizophrenia (Dickinson et al., 2007; Thuaire et al., 2020; Randers et al., 2021), and thus the subtest measuring reaction time was included.

Information processing speed was assessed with the 5-choice Reaction Time task (RTI), which assesses motor and mental response speed to a visual target appearing on the screen. A yellow spot appears randomly in one of the five locations, and the participant must react by releasing the button on the bottom of the screen and selecting the correct circle with the dot. The task is designed to measure movement time, reaction time, response accuracy, and impulsivity. RTI can be taken as a good measure of processing speed since it has been reported having high consistency with other neurocognitive measures of processing speed (Sexton et al., 2012). It also requires sustained visual attention (Gonçalves et al., 2016). The two RTI outcome measures included were the mean five-choice reaction time, which is the mean duration between the onset of the stimulus and the release of the button, and the mean five-choice movement time from releasing the button to touching the stimulus. Both measures chosen for the present study, consider only the correct answers.

Visual learning and memory were assessed with the Paired Associates Learning Task. In this task, boxes containing a pattern are displayed on the screen, and their contents are shown in a randomized order. After the contents of the boxes have been revealed, the subject is shown a pattern in the middle of the screen. They must select the box containing this pattern. There are four trials with increasing difficulty containing 2, 4, 6, and 8 patterns. Studies have demonstrated moderate correlations between the task and traditional pen-and-paper tests assessing visual memory, delayed recall, visuospatial attention, and working memory (Kim et al., 2009; Torgersen et al., 2012). The outcome variables included in this study were the adjusted number of total errors made in the four assessment problems, the number of correct box choices that were made on the first attempt during the different assessment problems, and the number of patterns in the last correct problem reached in the task.

2.4. Sociodemographic variables

Information on relationship status, living arrangements, education level, and self-rated depression and/or anxiety were included as background factors. Age of diagnosis refers to the age when the participant received their schizophrenia diagnosis. If the participant was married, in a registered partnership, or co-habiting, their marital status was coded as married. Level of education was classified in three categories based on the highest level of education, in line with an earlier Finnish population study protocol (Aromaa and Koskinen, 2004): low for comprehensive education, medium for upper secondary education, and high for higher education. Living in in-patient hospital housing, care facility, or supervised housing was considered as living in care, otherwise the participant was considered living independently.

2.5. Psychological distress

Self-rated depression or anxiety were assessed with the EQ-5D health-related quality of life questionnaire (Rabin and De Charro, 2001). One item about anxiety or depression was included ("I am not anxious or depressed", "I am moderately anxious or depressed", "I am extremely anxious or depressed"). This item was used to create a variable indicating whether the participant experiences either none or at least moderate anxiety or depression.

Psychological distress was measured with the five-item version of the Mental Health Inventory (MHI-5), which has reasonable validity and is considered an effective brief screening instrument for mood and anxiety disorders (Cuijpers et al., 2009). MHI-5 has a total score from 0 (poor mental health) to 100 (good mental health). The prevalence of severe psychological distress was determined with the cut-off point 52, which is most used in past research (Thorsen et al., 2013).

2.6. Statistical analysis

Statistical analyses were performed using R version 4.2.2 and the stats package (R Core Team, 2022). Group differences between those using antidepressant medications and those who did not were tested using t- and χ^2-tests. One-way analysis of covariance was used to check for differences in cognitive test results when the participants were grouped based on the type of antidepressant used.

To test associations between medication use and cognitive performance, linear regression models were built in which the outcome variables of the cognitive tests were separately inserted as the dependent variable. In the first phase, the use of antidepressants in general was inserted as an explanatory variable, along with controlling variables in two steps. In the second phase, the five different antidepressant types, benzodiazepines, and anticholinergic burden were used as explanatory variables. In both phases, only age and gender were controlled first, to identify crude associations. Then a more comprehensive array of controlling variables was added to adjust the models: age of diagnosis, whether the participant is living in care or independently, marital status, education coded as dummy variables, and self-rated anxiety or depression.

Since nearly all participants used antipsychotic medication (97,1 %), their use was not included as a separate controlling variable. We also did not include the number of antipsychotics used and psychological distress (MHI-5) as covariates, since these were strongly correlated with other covariates. Number of antipsychotics used was correlated with anticholinergic burden ($r = 0.75$, $p < .001$), and psychological distress with experienced anxiety or depression ($r = -0.62$, $p < .001$).

The distributions of mean reaction time and movement time were positively skewed with some extreme values. To control the possible effect of this, new reaction time variables were computed by replacing positive values that deviated over 2.5 standard deviations from the mean with the value at +2.5 SD (Miller, 1991). After this, the variables were transformed logarithmically. The analyses were performed also with these variables. This resulted in models with a slightly higher R^2. Since the results did not differ in relation to the research questions, only the original values are reported.

3. Results

3.1. Medication use

The characteristics of the study sample are described in Table 1. In all, 35.60 % ($n = 1198$) of the participants used antidepressant medicines regularly. On average, participants with active antidepressant medication were more likely to live in a care facility, they experienced more depression and/or anxiety, and psychological distress.

Most of those using antidepressants used only selective serotonin reuptake inhibitors ($n = 670$, 19.91 %). The second most common group was those using only serotonin-norepinephrine reuptake inhibitors ($n = 213$, 6.33 %), followed by mirtazapine ($n = 87$, 2.59 %), tricyclic antidepressants ($n = 62$, 1.84 %), and an assortment of other antidepressants ($n = 48$, 1.43 %). Altogether 116 participants used two different types of antidepressants, and 2 participants regularly used three different antidepressants. Benzodiazepines were used by 845 study participants (25.11 %). The benzodiazepines used by the participants were lorazepam ($n = 269$), oxazepam ($n = 194$), diazepam ($n = 181$), temazepam ($n = 157$), clonazepam ($n = 104$), chlordiazepoxide (n = 15), clobazam ($n = 7$), and midazolam (n = 1). Most participants (54.32 %) using benzodiazepines did not use antidepressants ($n = 459$). Altogether 386 participants concurrently used antidepressants and benzodiazepines.

The mean anticholinergic burden for all participants was 4.32 (SD = 2.62, range 0–18). The mean ACB score for those using antidepressants was 5.64 (SD = 2.55), which was significantly higher than the mean 3.58 (SD = 2.35) of those not using antidepressants (t[3363] = 23.62, $p < .001$). The participants used an average of 1.74 (SD = 1.10) antipsychotics, with most people only using one ($n = 1304$) or two ($n = 1036$).

Table 1
Sociodemographic characteristics and cognitive performance of all participants (age 18–70). Comparison between those who use and those who do not use antidepressant (right), *p*-value using t or χ^2 test as appropriate.

Characteristic	All	Not using antidepressants	Using antidepressants	p-value
N	3365	2167 (64.40 %)	1198 (35.60 %)	
Age, mean (SD)	45.02 (12.72)	44.84 (12.15)	45.12 (13.03)	t(3363) = 0.547
Age of diagnosis, mean (SD)	26.12 (8.09)	26.16 (8.44)	26.10 (7.89)	t(3363) = 0.825
Women, *N* (%)	1422 (42.26 %)	889 (41.02 %)	533 (44.49 %)	$\chi^2(1) = 0.056$
Intermediate or higher education	2138 (63.54 %)	1399 (64.56 %)	739 (61.89 %)	$\chi^2(1) = 0.105$
Married or cohabitating	474 (14.11 %)	311 (14.37 %)	163 (13.63 %)	$\chi^2(1) = 0.589$
Living in care facility	1034 (30.76 %)	620 (28.64 %)	414 (34.59 %)	$\chi^2(1) < 0.001$
Experiences anxiety or depression	1399 (41.85 %)	772 (35.91 %)	627 (52.56 %)	$\chi^2(1) < 0.001$
Experiences psychological distress (MHI-5)	862 (26.00 %)	483 (22.66 %)	379 (32.04 %)	$\chi^2(1) < 0.001$
Reaction Time (ms.), mean (SD)				
Mean reaction time	474 (123)	475 (127)	474 (116)	t(3363) = 0.792
Mean movement time	363 (157)	362 (162)	363 (148)	t(3363) = 0.811
Paired Associates Learning, mean (SD)				
Total errors adjusted	36.58 (20.13)	36.42 (20.16)	36.88 (20.08)	t(3363) = 0.525
First attempt memory score	7.48 (4.86)	7.56 (4.89)	7.33 (4.81)	t(3363) = 0.193
Number of patterns reached	6.27 (1.81)	6.29 (1.78)	6.24 (1.87)	t(3363) = 0.432

3.2. Reaction time and visual memory performance

The mean levels of reaction time and visual memory performance for all participants are presented in Table 1. No differences were found in either reaction time task (RTI) or the paired associates learning (PAL) task between those using antidepressants and those not. Similarly, there were no significant between-group differences in cognitive performance when grouping the participants based on the type of antidepressant used (Table 2).

Antidepressant use in general was not associated with reaction time and paired associates learning (Table A.1). When accounting for specific antidepressant types, SNRI antidepressant use was associated with cognitive performance (Tables 3 and 4). The use of SNRI medication was associated with a shorter mean reaction time (B = −20.56, $p = .010$) in the reaction time task and less errors (B = −2.46 $p = .048$) in the paired associates learning task. Only the association with the shorter mean reaction time remained significant when the controlling variables living in care, being married, education level, and self-reported depression or anxiety were included in the model (B = −16.97, $p = .033$). The size of this effect was very small ($\beta = -0.04$). Model fit when all the variables were included was low ($R^2 = 0.14$).

Table 2
Cognitive performance by CANTAB subscores for different antidepressant groups.

CANTAB mean (sd)	No antidepr. (*n* = 2167)	Mirtaz. (*n* = 87)	SSRI (*n* = 670)	SNRI (*n* = 213)	TCA (*n* = 62)	Other (*n* = 48)	Poly (*n* = 118)	p-value[a]
Reaction time (ms.)								
Mean reaction time (sd)	475 (127)	482 (101)	478 (120)	455 (92)	487 (157)	466 (73)	473 (129)	0.752
Mean movement time (sd)	362 (162)	387 (186)	364 (148)	349 (131)	368 (145)	384 (168)	359 (139)	0.617
Paired associates learning								
Total errors adjusted (sd)	36.42 (20.16)	40.52 (21.01)	37.32 (19.89)	34.36 (20.14)	40.08 (20.00)	34.58 (20.12)	35.54 (20.02)	0.607
First attempt memory score (sd)	7.56 (4.89)	6.84 (5.02)	7.23 (4.72)	8.01 (5.00)	6.23 (4.52)	7.29 (4.99)	7.66 (4.76)	0.128
Number of patterns reached (sd)	6.29 (1.78)	5.79 (2.00)	6.23 (1.85)	6.41 (1.79)	5.97 (2.03)	6.42 (1.93)	6.37 (1.90)	0.478

Note. A participant can only belong to one group, so those with multiple antidepressants are in group poly.
[a] One-way analysis of covariance with sex and age as covariates (df 6, 3356). Null hypothesis: the means are all equal.

Table 3
Associations between the medication variables and reaction time.

	Dependent variable: Reaction Time							
	Mean reaction time				Mean movement time			
	B	S	β	p	B	S	β	p
Step 1								
Mirtazapine	−0.61	9.95	0.00	0.951	0.15	12.45	0.00	0.991
SSRI	0.08	5.08	0.00	0.988	−7.06	6.36	−0.02	0.267
SNRI	−20.56	7.97	−0.04	0.010	−19.20	9.97	−0.03	0.054
TCA	−3.60	12.39	−0.01	0.771	−24.21	15.50	−0.03	0.118
Other	0.22	16.63	0.00	0.989	26.98	20.80	0.02	0.195
Benzodiazepines	23.20	5.03	0.08	<0.001	20.68	6.29	0.06	0.001
Antichol. burden	0.89	0.91	0.02	0.331	4.51	1.14	0.08	<0.001
Control variables								
Women	0.69	4.06	0.00	0.866	13.19	5.08	0.04	0.010
Age	3.00	0.16	0.31	<0.001	4.37	0.20	0.35	<0.001
Model fit (R^2)	0.11				0.15			
Step 2								
Mirtazapine	−1.73	9.86	0.00	0.861	−1.97	12.41	0.00	0.874
SSRI	0.60	5.03	0.00	0.906	−6.59	6.33	−0.02	0.298
SNRI	−16.97	7.94	−0.04	0.033	−17.47	10.00	−0.03	0.081
TCA	−2.12	12.20	0.00	0.862	−22.74	15.35	−0.03	0.139
Other	0.71	16.40	0.00	0.966	27.18	20.65	0.02	0.188
Benzodiazepines	20.08	5.00	0.07	<0.001	17.28	6.29	0.05	0.006
Antichol. burden	−1.23	0.92	−0.03	0.180	2.78	1.16	0.05	0.017
Control variables								
Women	5.62	4.11	0.02	0.171	17.49	5.17	0.06	<0.001
Age	3.17	0.18	0.33	<0.001	4.34	0.23	0.35	<0.001
Age of diagnosis	−0.72	0.28	−0.05	0.010	0.09	0.35	0.01	0.801
Living in care	38.61	4.58	0.15	<0.001	36.82	5.77	0.11	<0.001
Married	−12.11	5.85	−0.03	0.039	−11.16	7.37	−0.03	0.130
Medium educ.	−9.68	4.49	−0.04	0.031	−3.39	5.66	−0.01	0.549
High educ.	−15.79	6.02	−0.05	0.009	−16.15	7.58	−0.04	0.033
Depressed/anxious	6.28	4.15	0.03	0.130	8.78	5.22	0.03	0.093
Model fit (R^2)	0.14				0.16			

Linear regression models testing the association of various psychotropic medication variables with the two reaction time variables (B = unstandardized beta, S = standard error, β = standardized beta, effect size). In the first step, the five different antidepressant types, benzodiazepines, and anticholinergic burden were inserted as independent variables. Only age and gender were controlled. In the second step, more psychosocial controlling variables were introduced.

The use of benzodiazepines was associated with poorer performance in all outcome measures in the reaction time and paired associates learning (Tables 3 and 4). All but first attempt memory score and number of patterns reached in the paired associates learning task remained statistically significant after including the controlling variables living in care, being married, education level, and self-reported depression or anxiety.

Anticholinergic burden was associated with a significantly longer mean movement time in the reaction time task (B = 4.51, p < .001). This association remained significant when the controlling variables were added to the model (B = 2.78, p = .017). In the paired associates learning task, higher anticholinergic burden was associated with poorer performance in all outcomes, even after controlling the psychosocial variables.

4. Discussion

In this study, conducted in a large clinical sample of patients with schizophrenia, 36 % used antidepressant medication. In line with our hypothesis, the use of antidepressant medication in general was not associated with reaction time and visual learning. Our hypothesis on the association of mirtazapine use and better cognitive performance did not

Table 4
Associations between the medication variables and paired associates learning.

Dependent variable: Paired Associates Learning												
	Total errors adjusted				First attempt memory score				Number of patterns reached			
	B	S	β	p	B	S	β	p	B	S	β	p
Step 1												
Mirtazapine	−1.74	1.55	−0.02	0.261	0.55	0.38	0.02	0.14	0.02	0.14	0.00	0.881
SSRI	−1.01	0.79	−0.02	0.201	0.17	0.19	0.02	0.364	0.10	0.07	0.02	0.177
SNRI	−2.46	1.24	−0.32	0.048	0.58	0.30	0.03	0.054	0.18	0.12	0.03	0.124
TCA	−2.46	1.93	−0.02	0.203	0.35	0.47	0.01	0.451	0.21	0.18	0.02	0.232
Other	0.07	2.59	0.00	0.978	−0.67	0.63	−0.02	0.283	0.02	0.24	0.00	0.929
Benzodiazepine	2.16	0.78	0.05	0.006	−0.46	0.19	−0.04	0.016	−0.16	0.07	−0.04	0.025
Antichol. burden	0.95	0.14	0.12	<0.001	−0.25	0.03	−0.13	<0.001	−0.08	0.01	−0.12	<0.001
Control variables												
Women	−3.48	0.63	−0.09	<0.001	0.74	0.15	0.08	<0.001	0.29	0.06	0.08	<0.001
Age	0.64	0.03	0.40	<0.001	−0.15	0.01	−0.40	<0.001	−0.05	0.00	−0.35	<0.001
Model fit (R^2)	0.20				0.19							0.15
Step 2												
Mirtazapine	−2.02	1.52	−0.02	0.182	0.60	0.37	0.03	0.105	0.06	0.14	0.01	0.673
SSRI	−0.86	0.77	−0.02	0.264	0.14	0.19	0.01	0.465	0.09	0.07	0.02	0.201
SNRI	−1.61	1.22	−0.02	0.188	0.38	0.30	0.02	0.205	0.10	0.11	0.01	0.388
TCA	−2.24	1.87	−0.02	0.232	0.30	0.46	0.01	0.505	0.19	0.17	0.02	0.266
Other	0.33	2.52	0.00	0.897	−0.75	0.61	−0.02	0.221	0.01	0.23	0.00	0.975
Benzodiazepine	1.52	0.77	0.03	0.048	−0.33	0.19	−0.03	0.081	−0.11	0.07	−0.03	0.118
Antichol. burden	0.58	0.14	0.08	<0.001	−0.16	0.03	−0.0.09	<0.001	−0.05	0.01	−0.07	<0.001
Control variables												
Women	−2.37	0.63	−0.06	<0.001	0.45	0.15	0.05	0.004	0.21	0.06	0.06	<0.001
Age	0.70	0.03	0.44	<0.001	−0.16	0.01	−0.43	<0.001	−0.06	0.00	−0.39	<0.001
Age of diagnosis	−0.21	0.04	−0.09	<0.001	0.05	0.01	0.08	<0.001	0.02	0.00	0.09	<0.001
Living in care	5.74	0.70	0.13	<0.001	−1.37	0.17	−0.13	<0.001	−0.60	0.07	−0.15	<0.001
Married	−1.41	0.90	−0.02	0.118	0.56	0.22	0.04	0.011	0.00	0.08	0.00	0.997
Medium educ.	−2.87	0.69	−0.07	<0.001	0.71	0.17	0.07	<0.001	0.26	0.06	0.07	<0.001
High educ.	−6.42	0.93	−0.12	<0.001	1.46	0.23	0.12	<0.001	0.52	0.09	0.11	<0.001
Depressed/anxious	0.46	0.64	0.01	0.473	−0.06	0.16	−0.01	0.681	−0.05	0.06	−0.01	0.399
Model fit (R^2)	0.24				0.23							0.20

Linear regression models testing the association of various psychotropic medication variables with the three visual learning test variables (B = unstandardized beta, S = standard error, β = standardized beta, effect size). In the first step, the five different antidepressant types, benzodiazepines, and anticholinergic burden were inserted as independent variables. Only age and gender were controlled. In the second step, more psychosocial controlling variables were introduced.

gain support. However, the use of SNRI antidepressant medication was associated with a slightly better performance in the reaction time and visual memory tasks. The association with faster mean reaction time remained significant even when various controlling factors were introduced. We also found that 25 % of participants used benzodiazepines and that the mean anticholinergic burden of all the medications used by the participants was high. Benzodiazepine use and higher anticholinergic burden were associated with poorer reaction time and visual learning performance.

In the present study, participants using antidepressant medication experienced higher burden of disease than those who did not use antidepressants. They lived more often in a care facility with full- or part-time support and report higher levels of anxiety and depression. The anticholinergic burden of the medication used by all participants was relatively high (4.32) when compared to an earlier study of patients with schizophrenia with an ACB score of 3.8 (Joshi et al., 2021). In older adults in the general population, even an ACB score of 3 may be associated with a risk of developing dementia (Coupland et al., 2019).

Previous research on the association between antidepressant use and cognitive performance in schizophrenia has been ambiguous. Our study is in line with prior studies that found no clinically meaningful association between antidepressant use in general and cognitive performance (Vernon et al., 2014). Even though antidepressant medication is beneficial in many other aspects (Helfer et al., 2016), their use as such is not associated with better cognitive performance. On the other hand, antidepressant use did not associate with worse cognitive performance either and thus they can be considered safe from this perspective.

Some earlier randomized controlled studies have demonstrated a favorable effect of mirtazapine use on cognitive performance in schizophrenia (Stenberg et al., 2010, 2011; Cho et al., 2011; Delle Chiaie et al., 2017). This effect was not found in our study as was also the case in one previous RCT (Berk et al., 2009). This discrepancy may be due to the different cognitive assessment methods used. For instance, when looking at memory performance, some earlier studies found that mirtazapine had a favorable effect on immediate and delayed memory in tasks involving vocabulary and stories (Cho et al., 2011; Delle Chiaie et al., 2017), while our study only measured visual memory. Furthermore, the discrepancy may be related to the heterogeneity of the sample in the present study when compared to earlier studies. In earlier research, the favorable effect of mirtazapine has been demonstrated with hard-to-treat patients (Stenberg et al., 2010, 2011), while our sample was more diverse. Furthermore, when comparing with the mirtazapine RCTs, in the present study the dosage of mirtazapine used by the participants was not controlled. This is relevant since mirtazapine may have also been prescribed in lower dosages to treat insomnia.

Moreover, it is important to consider that participants using antidepressants had a higher burden of disease, which is potentially linked to poorer cognitive performance. Therefore, one may hypothesize that if a patient already had lower cognitive performance due to high burden of disease, the association of SSRI or other antidepressants with better cognition might go undetected.

In the present study, SNRI antidepressant use was associated with faster reaction time. The finding is in line with an earlier study demonstrating that serum levels of the SNRI venlafaxine plus *O*-desmethylvenlafaxine were associated with better cognitive performance (Steen et al., 2015). Earlier studies have also found that among clinical populations other than schizophrenia SNRI antidepressants may be associated with improvements in cognitive performance (Biringer et al., 2009; Greer et al., 2014; Castellano et al., 2016). SNRI antidepressants differ mechanistically from most other antidepressants since they function as norepinephrine reuptake inhibitors. Our study setting does not allow making inferences about possible neuropharmacological

mechanisms. However, interestingly there is evidence among patients with schizophrenia that atomoxetine, a noradrenaline reuptake inhibitor used for ADHD, may improve cognitive symptoms (Solmi et al., 2019). While the association between the usage of SNRI medicines and faster reaction time in our study was statistically significant, the average difference in reaction time was very small. Therefore, the clinical significance of the finding is unclear. Nevertheless, it warrants future research.

Thus far, our study contains one of the largest samples investigating the association between antidepressant use and cognitive performance in schizophrenia. While many previous studies have been randomized controlled trials allowing inference of causality, their sample sizes have been small. Moreover, the SUPER-cohort is a real-world clinical sample containing a nationwide Finnish heterogeneous set of patients. This increases the clinical importance and generalizability of the results.

This study does not allow the inference of causation. In other words, we cannot determine whether the significant associations between SNRI medications and benzodiazepines and cognitive performance are causally related to the usage of those medicines. Especially in the case of benzodiazepines, it is also possible that the association is based on other qualities of the group of individuals to whom the medications are prescribed. These participants may already exhibit worse cognitive problems related to their other symptoms. Nevertheless, since we were able to control for several other factors associated with cognition, a causal explanation remains possible and warrants future research. A causal explanation would be in line with earlier research demonstrating an association between benzodiazepine use and other adverse outcomes (Fontanella et al., 2016; Taipale et al., 2021).

A core limitation of our study is that the cognitive assessment was brief. Only two CANTAB subtests were included, and the assessment method utilized only one medium (tablet computer) emphasizing visuospatial performance. This left relevant cognitive functions, such as verbal ability and memory, delayed recall, working memory, executive function, and perceptual reasoning, largely outside the assessment. Nevertheless, especially information processing speed, assessed with a reaction time test in this study, can be used as an indicator of overall cognitive performance. There is evidence placing processing speed at the core of cognitive impairment in schizophrenia (Dickinson et al., 2007; Thuaire et al., 2020). A further limitation of this study was that medications were self-reported, and the dosages were not included. However, extra care was used to confirm the medicines from external sources when possible. It has also been demonstrated that in Finland the concordance between self-reported medication and information obtained from the official prescription database is high (Haukka et al., 2007). It is also possible that adherence varies for different medication types, even though we made an effort control this. A third limitation is that we could not calculate chlorpromazine-equivalent scores for the antipsychotics used by the participants. However, we did include the anticholinergic burden scale, which includes most of the commonly used antipsychotic medications. This score correlated strongly with the number of antipsychotics used. Therefore, whether it is due to the specific anticholinergic effect or the concurrent usage of multiple antipsychotics, it is evident that this is associated with worse cognitive performance.

This study has four clinical implications. First, our results together with earlier studies suggest that prescribing patients with schizophrenia antidepressant medication does not generally associate with better or worse cognitive performance. The analysis also suggests that those using SNRI antidepressants may have a slightly better cognitive performance, but since this effect is very small, it should be investigated further with more rigid experimental designs. Second, the use of benzodiazepines was common among patients with schizophrenia and was associated with poorer performance in reaction time and visual learning. These findings add to the caution of prescribing benzodiazepines. Although they may be necessary in short-term for some, their regular long-term use may be detrimental to cognitive performance (Barker et al., 2004). Third, the mean anticholinergic burden of the medications used by patients in our study was high when compared to earlier studies (Hsu et al., 2017; Joshi et al., 2021). The anticholinergic burden was associated with a poorer cognitive performance. In clinical practice, more attention should be paid to the potential anticholinergic burden of medications. The ACB scale offers an easy practical tool for this. Fourth, our study demonstrates that many psychosocial variables associate with cognitive performance. For example, whether the patients were living by themselves or in care was significantly associated with cognitive performance. Poorer cognitive and functional capacity is associated with a need for more intensive care, and thus living arrangements should be considered in studies where in- and outpatients are combined. These findings highlight that several psychosocial factors lie behind the variability observed in the neurocognitive performance of patients with schizophrenia.

In conclusion, the relationship between cognitive symptoms of schizophrenia and antidepressant medication remains elusive. Patients with and without antidepressants performed similarly in cognitive tasks. However, we found an association of SNRI antidepressants with faster reaction time, which warrants more investigation in the future. Our study highlights that the patients requiring antidepressant medicines may have worse psychosocial problems and lower well-being than those who do not use antidepressant medicines. This should be considered in planning treatment and rehabilitation. Lastly, this study corroborates the increasing caution in prescribing benzodiazepines for regular use, and the need to consider the overall anticholinergic load of medications in clinical practice.

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Ville Mäkipelto: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Annamari Tuulio-Henriksson:** Supervision, Writing – review & editing, Data curation, Project administration. **Christian Hakulinen:** Supervision, Writing – review & editing. **Solja Niemelä:** Data curation, Writing – review & editing, Project administration. **Markku Lähteenvuo:** Data curation, Writing – review & editing, Project administration. **Asko Wegelius:** Data curation, Writing – review & editing, Project administration. **Tuula Kieseppä:** Data curation, Writing – review & editing, Project administration. **Erkki Isometsä:** Data curation, Writing – review & editing, Project administration. **Jari Tiihonen:** Data curation, Writing – review & editing, Project administration. **Olli Kampman:** Data curation, Project administration, Writing – review & editing. **Kaisla Lahdensuo:** Writing – review & editing. **Atiqul Mazumder:** Writing – review & editing. **Jaana Suvisaari:** Data curation, Project administration, Writing – review & editing. **Minna Holm:** Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2024.02.025.

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