Lifetime use of psychiatric medications and cognition at 43 years of age in schizophrenia in the Northern Finland Birth Cohort 1966

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Abstract

Background: Higher lifetime antipsychotic exposure has been associated with poorer cognition in schizophrenia. The cognitive effects of adjunctive psychiatric medications and lifetime trends of antipsychotic use remain largely unclear. We aimed to study how lifetime and current benzodiazepine and antidepressant medications, lifetime trends of antipsychotic use and antipsychotic polypharmacy are associated with cognitive performance in midlife schizophrenia.

Methods: Sixty participants with DSM-IV schizophrenia from the Northern Finland Birth Cohort 1966 were examined at 43 years of age with an extensive cognitive test battery. Cumulative lifetime and current use of psychiatric medications were collected from medical records and interviews. The associations between medication and principal component analysis-based cognitive composite score were analysed using linear regression.

Results: Lifetime cumulative DDD years of benzodiazepine and antidepressant medications were not significantly associated with global cognition. Being without antipsychotic medication (for minimum 11 months) before the cognitive examination was associated with better cognitive performance ($p=0.007$) and higher lifetime cumulative DDD years of antipsychotics with poorer cognition ($p=0.020$), when adjusted for gender, onset age and lifetime hospital treatment days. Other lifetime trends of antipsychotic use, such as a long antipsychotic-free period earlier in the treatment history, and antipsychotic polypharmacy, were not significantly associated with cognition.

Conclusions: Based on these naturalistic data, low exposure to adjunctive benzodiazepine and antidepressant medications does not seem to affect cognition nor explain the possible negative effects of high dose long-term antipsychotic medication on cognition in schizophrenia.

Keywords: schizophrenia, cognition, medication, benzodiazepine, antidepressant, antipsychotic, polypharmacy, adverse effect

1. Introduction

Antipsychotic medication forms the foundation of the evidence-based pharmacological treatment of schizophrenia [1, 2]. Antipsychotic polypharmacy, defined as the concomitant use of 2 or more antipsychotics, and other psychiatric medications, such as benzodiazepines and antidepressants, are also widely used in schizophrenia, especially in case of incomplete treatment response or comorbid psychiatric symptoms, although their indications and efficacy are less clear [3, 4, 5]. Neurocognitive deficits are a central dimension of schizophrenia, emerging during deviant neurodevelopment [6], being established by the first psychotic episode and staying relatively stable during the illness course for up to 10 years [7, 8, 9] and also in older persons with schizophrenia [10]. Because of the key role of these deficits in influencing the long-term outcome in schizophrenia [11], it is important to study the safety and effects of medication on cognition.

Antipsychotics have been associated with mild to moderate, positive cognitive effects in short-term randomised, controlled trials (RCTs) [12, 13, 14], possibly mostly explained by practice effects [15]. Very little is known of the long-term cognitive effects of antipsychotics in schizophrenia after 2-3 [16] or 5 years of use [17]. In naturalistic studies, higher antipsychotic doses [18, 19, 20] or antipsychotic polypharmacy [19] have been associated with poorer cognition, and dose-reduction with improved cognition [21, 22].

Benzodiazepines are used by patients with schizophrenia for sedation, to treat anxiety and agitation or to combat adverse effects of antipsychotics [23]. There is no evidence of efficacy against psychotic symptoms [24] and there are concerns about the long-term safety of benzodiazepines, which have been associated with higher mortality in schizophrenia [23, 25]. Long-term use of benzodiazepines (mean 10 years) has been associated with cognitive impairment in a meta-analysis [26]. In schizophrenia cognitive improvement has been reported after the reduction of long-term (mean 4-11 years) benzodiazepine use [27, 28].

Antidepressants have some efficacy in reducing depressive [29] and negative [30] symptoms in schizophrenia, and moderate to high antidepressant exposure has been linked to lower mortality [25]. The cognitive effects of antidepressants in schizophrenia, studied in clinical trials ranging from 4 to 24 weeks in duration, have been positive, but clinically non-significant in one recent meta-analysis [31] and review [32].

The long-term effects of psychiatric medications in schizophrenia are mostly unknown. Studies on the lifetime use of psychiatric medications are rare and limited to antipsychotic medication largely ignoring other psychiatric medications. Double-blind RCTs of long-term treatment are the golden standard for the study of treatment effects, but difficult to carry

out for several years. Naturalistic, observational samples offer a feasible setting to investigate the long-term effects of medication [33] and form at least hypotheses for further study.

Pharmacoepidemiology has been a major study arm of the Northern Finland Birth Cohort 1966 (NFBC 1966) [34]. We previously showed that higher lifetime cumulative doses of antipsychotic medication were associated with a decline in verbal learning and memory between ages 34 and 43 years [17] and poorer global cognitive performance at the age of 43 years in schizophrenia [16]. However, prior research, including our own, has mainly focused on associations between cognition and antipsychotic medication, and we have not fully considered the possible effects of other psychotropic medication. In this study therefore, we aimed to investigate, for the first time, how lifetime cumulative and cross-sectional doses of benzodiazepine and antidepressant medications are associated with cross-sectional, global cognition in schizophrenia at 43 years of age. We also wanted to prose the effects of lifetime use of antipsychotics, and especially antipsychotic polypharmacy, on cognition in more detail than in our previous studies. We hypothesised that higher benzodiazepine and antipsychotic use, and antipsychotic polypharmacy, would be associated with poorer cognition and antidepressant use with neutral or positive cognitive effects, when potential confounders were taken into account.

2. Methods

2.1 Sample

2.1.1 Participants

The participants were derived from the unselected, general population based Northern Finland Birth Cohort 1966 (NFBC 1966) that consists of 12 058 live-born children [35]. The NFBC 1966 members with a lifetime psychosis diagnosis were detected from national register data by the end of 2008 and questionnaire data collected in 1997 [36]. Persons with a psychosis diagnosis in the Care Register for Health Care, in the Social Insurance Institution of Finland registers on sick leaves, disability pensions or the right to reimbursement for psychoactive medication due to psychosis and those who reported a psychosis or current antipsychotic use were included.

This procedure, described in more detail in our earlier work [16], resulted in 257 NFBC 1966 members with a lifetime psychosis diagnosis and known address, who were invited. Ninety-nine persons (38.5%) participated in a psychiatric examination in 2008-2011 including the SCID I interview leading to DSM-IV lifetime diagnosis. There were 60 (87.0%)

persons with a diagnosis of schizophrenia spectrum disorder, a completed cognitive test battery and information on lifetime antipsychotic medication. Of them 50 (83%) had a DSM-IV lifetime diagnosis of schizophrenia, 6 (10%) schizoaffective, 2 (3%) schizophreniform and 2 (3%) delusional disorder. In this article, hereafter, the term schizophrenia encompasses schizophrenia and other schizophrenia spectrum disorders. Lifetime antipsychotic dose and cognition at 43 years of age has been studied in this same sample before [16] and a subsample of it (40 cases, 67%) was analysed in another study on lifetime antipsychotic medication and change of verbal learning and memory between 34 and 43 years [17].

There was selective attrition of participants in educational level, onset age, disability pension status and schizophrenia diagnosis, but weighted sensitivity analyses performed in an earlier study of this sample [16] confirmed that attrition did not significantly affect the results on cumulative lifetime antipsychotic medication dose and global cognition at age 43 years.

2.1.2 Ethical considerations

The Ministry of Social and Health Affairs gave permission to collect data for the NFBC 1966 study. The Ethical Committee of the Northern Ostrobothnia Hospital District regularly reviews the study. All participants gave informed consent. The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans was followed.

2.2 Data on psychiatric medication

Information on the lifetime use of psychiatric medications until the 43-year examination date was collected during 2007-2016 from all available Finnish hospital and outpatient records. Data collection of antipsychotic medication, described in detail elsewhere [17, 37], was completed in 2014 and collection of other psychiatric medications in 2016. These data were supplemented with information on current (last 3 months) and earlier use of psychiatric medications obtained in an interview in the 43-year study [38] and register of the Social Insurance Institution of Finland on psychoactive medications purchased in 1997. Based on this information the cumulative lifetime and current doses of psychiatric medications were calculated.

2.3 Neurocognitive assessment

The neuropsychological examination was performed at the 43-year study using an extensive neuropsychological battery of tests comprising the Abstraction Inhibition and Working Memory task (AIM) [39], California Verbal Learning Test (total scores of trials 1-5; CVLT) [40], Visual Object Learning Test (VOLT) [41], Verbal fluency [42], Visual series (WMS-III) [43], and Vocabulary, Digit Span and Matrix reasoning (WAIS-III) [44].

2.4 Variables

2.4.1 Neurocognitive variables and the cognitive composite score

A principal component analysis (PCA) of the eight chosen neurocognitive test variables resulted in a cognitive composite score representing global cognitive performance (see 2.5 Statistical analyses) [16].

2.4.2 Medication variables

The psychiatric medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system [45] into benzodiazepines (including benzodiazepine derivatives N05BA, N03AE and N05CD; and benzodiazepine related drugs N05CF), antidepressants (N06A), antipsychotics (N05A), anticholinergic agents (N04A) and other psychiatric medication.

The medication variables representing lifetime and current use are described in detail in Table 1. The current doses were transformed to Defined Daily Dose ratios (DDD ratios) and cumulative exposure to Defined Daily Dose years (DDD years) [45].

2.4.4 Background variables

The analyses were adjusted for relevant background variables and confounders, including gender, age of illness onset, markers of severity of illness (logarithmic transformation of cumulative lifetime psychiatric hospital treatment days until the study, and remission and PANSS positive, negative and disorganisation symptoms, classified based on the factor structure described by van der Gaag et al. [46], at the time of the study), educational level (Supplementary material, Methods) and current antipsychotic dose and benzodiazepine and antidepressant use (Table 1).

2.5 Statistical analyses

The measure of global cognitive performance was derived from a principal component analysis (PCA) of the cognitive test variables (Immediate free recall of trials 1–5 of CVLT, total scores of VOLT, AIM, Verbal fluency, Visual series, Vocabulary, Digit Span and Matrix reasoning). Missing values of the cognitive tests (one case was missing an AIM score, 2 a VOLT score and 3 both VOLT and AIM scores) were predicted using multiple imputation (20 datasets) [47] with fully conditional specification (MCMC) method and linear regression as model type using data from all eight cognitive test variables. The PCA (eigenvalue set as >1) resulted in one cognitive factor (cognitive composite score), which explained 52.9% of total variance. Communalities were between 0.32 and 0.66 and factor loadings between 0.57 and 0.81.

The associations between the cognitive composite score and psychiatric medication variables were analysed using linear regression analysis. The natural logarithm of DDD years of lifetime psychiatric medications to correct for their skewness and non-transformed other psychiatric medication variables were used as predictor variables. The effects of medication variables in the linear regression models are presented as unstandardised regression coefficients (B) and their standard error (SE), standardised regression coefficients (Beta) and p-values. As post hoc analyses, the means of the composite score with 95% confidence intervals were plotted in the high-, medium- and low-dose groups of the cumulative DDD years of medication (divided based on tertiles). P-values < 0.05 were considered statistically significant. The analyses were performed using IBM SPSS Statistics 24 [48].

3. Results

3.1 The characteristics of the sample

The characteristics of the sample are described in Table 2. The sample consisted of 60 cases (33 males, 55%) with lifetime schizophrenia. The mean duration of illness of the sample was 16.5 years (SD 6.0) and average age was 43.1 years (SD 0.8).

3.2 The characteristics of medication use

The lifetime and current use and doses of antipsychotic, benzodiazepine and antidepressant medications are presented in Table 3. During lifetime antipsychotics were used by 98% of cases, benzodiazepines by 72% and antidepressants by 42% and at the time of the study by 85%, 38% and 22% respectively. The lifetime and current use and doses of specific medication agents are presented in Supplementary Table 1.

3.3 The association between lifetime and current benzodiazepine and antidepressant medications and global cognition

Lifetime cumulative DDD years of benzodiazepines or antidepressants, current DDD ratios and use of benzodiazepines or antidepressants at the time of the study were not significantly associated with global cognition (Table 4). In the post-hoc analyses illustrated in Figure 1, those with high or medium lifetime DDD years of benzodiazepines had poorer global cognition than those with low lifetime DDD years. However, both low and high lifetime antidepressant doses were associated with better global cognitive performance than medium doses.

3.4 The association between lifetime and current antipsychotic medication and global cognition

Being without antipsychotic medication (range 0.9-20.3 years, mean 8.7 years) before the cognitive examination (n=9) was associated with better global cognitive performance ($p=0.012$), also when adjusted for gender and age of illness onset ($p=0.006$) or several other covariates, including illness severity measures (Table 5). Having long antipsychotic-free periods during treatment, excluding the time of cognitive examination (n=20), was not associated with global cognition (Table 5). A higher proportion of time with antipsychotic use during the illness course, a higher proportion of time on antipsychotic polypharmacy, a higher current DDD ratio of antipsychotic medication and higher current antipsychotic polypharmacy had significant unadjusted associations with poorer global cognition, but not when adjusted (Table 5).

Higher lifetime antipsychotic DDD years were significantly associated with poorer global cognition ($p<0.001$), when adjusted for gender, age of illness onset ($p=0.018$) and several other covariates (Table 5). The lifetime antipsychotic exposure of those who did not use antipsychotics at the cognitive examination was lower than in the rest of the sample (median 0.3 vs. 14.2 DDD years respectively). In the post hoc analyses, high and medium lifetime DDD years of antipsychotics were associated with poorer global cognition than low lifetime doses (Figure 1).

4. Discussion

4.1 Main results

Lifetime and current doses of benzodiazepine and antidepressant medications were not significantly associated with global cognition. Not using antipsychotic medication for a relatively long time before the cognitive examination was associated with better global cognitive performance. However, antipsychotic-free periods of at least one year earlier

during treatment were not associated with cognition. Other lifetime trends of antipsychotic use, current antipsychotic dose or polypharmacy were not significantly associated with cognition in adjusted models.

4.2 Comparison with previous studies

Benzodiazepines have been associated with cognitive impairment, both after acute administration [49] and in the long-term treatment in a diagnostically heterogeneous sample [26]. Even with some degree of cognitive recovery, found also in schizophrenia after tapering or withdrawal of long-term benzodiazepine treatment [27, 28], the impairments persist [50]. Despite a paucity of studies conducted in schizophrenia and differences in exposure (use of benzodiazepines vs. cumulative dose, withdrawal vs. continued use) and setting (heterogeneous clinical vs. naturalistic sample), our results do not support the earlier findings of the association between use of benzodiazepines and poorer cognition.

The short-term cognitive effects of antidepressants have been positive but clinically negligible [31, 32]. Not finding an association between cross-sectional or longitudinal, several years of antidepressant exposure and cognition is in line with the previous research.

Our findings could indicate that benzodiazepines and antidepressants do not have strong cognitive effects in schizophrenia, but other explanations are also possible. In the subsample of 43 benzodiazepine and 25 antidepressant users, the lifetime exposure was relatively small (0.25 DDDs of benzodiazepines and 0.19 DDDs of antidepressants per year during the whole illness duration), which may remain under a threshold that could cause permanent, non-reversible cognitive effects. Additionally, most persons in our sample had used several medications and antipsychotics more than other medications, making it difficult to separate the effects of benzodiazepines and antidepressants.

Antipsychotics have minimal cognitive effects in schizophrenia during the first years of treatment [7]. Antipsychotic polypharmacy has been connected with both negative [19] and neutral cognitive effects [51], but not with higher mortality than antipsychotic monotherapy [52]. A number of studies have documented associations between high-dose, long-term antipsychotic exposure and changes in the brain volume [53, 54, 55], functioning [56] and cognition [57, 16]. The association between higher lifetime antipsychotic DDD years and poorer cognition was not a novel finding, as we reported it in our prior study using chlorpromazine equivalent dose-years [17]. The method of measuring drug exposure did not significantly influence the main results, even though discrepancy has been found between chlorpromazine and DDD-equivalence estimations [58].

The finding indicating that being without antipsychotics for a relatively long time before the cognitive examination is associated with better cognitive functioning, but antipsychotic-free periods at any other time during the treatment were not, can be seen to further support the view that antipsychotics do influence cognitive functioning in schizophrenia, but their cognitive effects may not be irreversible.

Earlier studies have also identified a subpopulation of persons with schizophrenia who manage for many years with a lower dose or without antipsychotic medication and have markers of less severe illness [59] or better functional outcome [60]. In the NFBC 1966 being antipsychotic-free [61], having low cumulative lifetime antipsychotic dose or no drug-free periods of at least a month have also been associated with better functioning in midlife schizophrenia [37]. It is also likely that the persons in the current study (n=9), who managed for a long time (some for several years) without antipsychotics belong to this subgroup with a less severe illness course, perhaps a lower relapse risk and better preserved cognitive functioning. Also their lifetime exposure to antipsychotics was significantly lower than the exposure of the rest of the sample. Thus the finding of lower lifetime dose and better cognition may be related to a group of persons who do not use antipsychotics at the time of cognitive examination.

Most patients with schizophrenia have a significantly higher relapse risk without antipsychotic medication [2, 62] and recurrent or persistent psychosis has been posited to be detrimental to cognition [63]. Treatment algorithms recommend maintenance antipsychotic treatment especially with multiple psychotic episodes, but also give room to controlled dose tapering and discontinuation strategies [2].

4.3 Theoretical discussion

The cognitive effects of pharmacological agents rise from their potential to disrupt neurotransmission in areas of the brain responsible for cognitive functioning [49]. The cholinergic system projecting to the cortex and hippocampus is involved with memory, perception and attention. Anticholinergic qualities of medications, including many antipsychotic and antidepressant agents, impair cognitive functions and alterations in cholinergic function may mediate even longer-term adverse cognitive effects [64]. The short-term and long-term negative cognitive effects of benzodiazepines may relate to the potentiation of y-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain [65]. The properties of antipsychotics, especially D2 antagonism with high-potency or high-occupancy binding due to high-dose exposure and glutaminergic inhibition by 5-TH-2A antagonism have been hypothesised to worsen the mesocortical hypodopaminergic state behind negative and cognitive symptoms in schizophrenia [66, 67, 68].

Antidepressants have been theorised to improve cognition via enhanced serotonergic, adrenergic and dopaminergic transmission, based on the mechanisms of specific agents, and less expected benefits with agents of higher anticholinergic activity, such as tricyclic antidepressants, but no relevant improvement has been observed adjunctive to antipsychotic treatment [31]. In the long-term use of benzodiazepines the development of tolerance to sedative effects [69] could possibly reduce the cognitive effects.

4.5 Strengths and limitations

The strength of this study is the naturalistic, non-selected sample with wide-ranging, reliable, prospective information based on interviews, medical records and linkage to register data. The longitudinal data on lifetime exposure to and timing of use of psychiatric medications are unique. Utilising DDD equivalents available for all medications instead of chlorpromazine equivalents has the benefit that they are more frequently updated and based on wider usage data [58]. Selection bias in this epidemiologically sound sample is minimised in comparison with selected, clinical populations and the results may be more generalisable to real-world schizophrenia. The attrition bias was also analysed thoroughly and it is unlikely that it would affect the results [16].

A limitation is the comparatively small sample size, especially in the subgroups of benzodiazepine and antidepressant users, which limits the power to detect the effects of medication and rule out type II error. Because of multiple medication variables analysed, the likelihood that some of the significant results may be chance findings can increase. Adherence could also reduce the reliability of the medication data. Access to medical records and not only registers on prescriptions or purchases has enabled taking known antipsychotic-free periods and measures of adherence into account resulting in considerably reliable cumulative antipsychotic variables accepted before in several peer-reviewed publications [16, 17, 37, 55]. It would be relevant to analyse the cognitive effects of individual medications, instead of groups with heterogeneous mechanisms of action, and other psychiatric medications, such as mood stabilisers, but the sample size and use of many different medications by the same person during their lifetime did not allow for more detailed analyses. Two persons had used up to 14 different antipsychotic agents during their lives [16]. Also global cognitive performance may have been too insensitive to detect the effects of medications.

Naturalistic studies are limited in showing causality, yet they may be optimal and the only realistic option to study long-term exposure to medications [33]. Longitudinal assessment of global cognition and symptoms, of which we do not have available data, could have enabled a more refined analysis of cognitive trajectories related to the illness process and

other factors such as treatment. However, owing to our extensive database, we were able to control for a variety of most potential confounders associated with illness duration and both longitudinal and current severity at the time of the study and significantly reduce the risk of residual confounding. In this sample, transversal measurements reflect also longitudinal course: key areas of cognition [70] and antipsychotic medication [37] were quite stable in midlife. It is still possible that higher antipsychotic doses are given to those with a more severe or earlier onset illness and mark this more unfavourable illness course rather than cause poorer cognition. Similarly, managing without antipsychotics for many years may be a marker of a milder illness, which is also associated with preserved cognition. The possibility that long-term high-dose antipsychotic treatment could worsen cognitive deficits related to schizophrenia, supported by cumulating findings, should also be taken seriously.

Interpretation of the findings of this study concerning the safety of long-term benzodiazepine and antidepressant use that was very low in our sample or risks and benefits of antipsychotic discontinuation should be cautious. Further study in larger populations of the long-term exposure to and optimal treatment strategies of psychiatric medications in schizophrenia is needed for clinical implications as well as identifying markers of a subpopulation that may manage with smaller doses or even without antipsychotic medication.

4.6 Conclusions

Polypharmacy continues to be a common practice in the treatment of schizophrenia and regular critical evaluation of medication is required to reduce it. To our knowledge, this is the first report on the association between lifetime cumulative benzodiazepine and antidepressant exposures and cognition in midlife schizophrenia. Based on these naturalistic data, low exposure to adjunctive benzodiazepine and antidepressant medications does not seem to greatly affect cognition nor explain the cognitive effects of antipsychotic medication in schizophrenia.

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Disclosure of interest

J.H. Barnett is an employee of and shareholder in Cambridge Cognition, a cognitive assessment company. P.B. Jones has been a member of Roche and Otsuka Scientific Advisory Boards 2012-2014. All other authors declare that they have no conflicts of interest.

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Figure titles

Figure 1. Global cognition in low-, medium- and high-dose groups of lifetime cumulative DDD years of antipsychotics, benzodiazepines and antidepressants

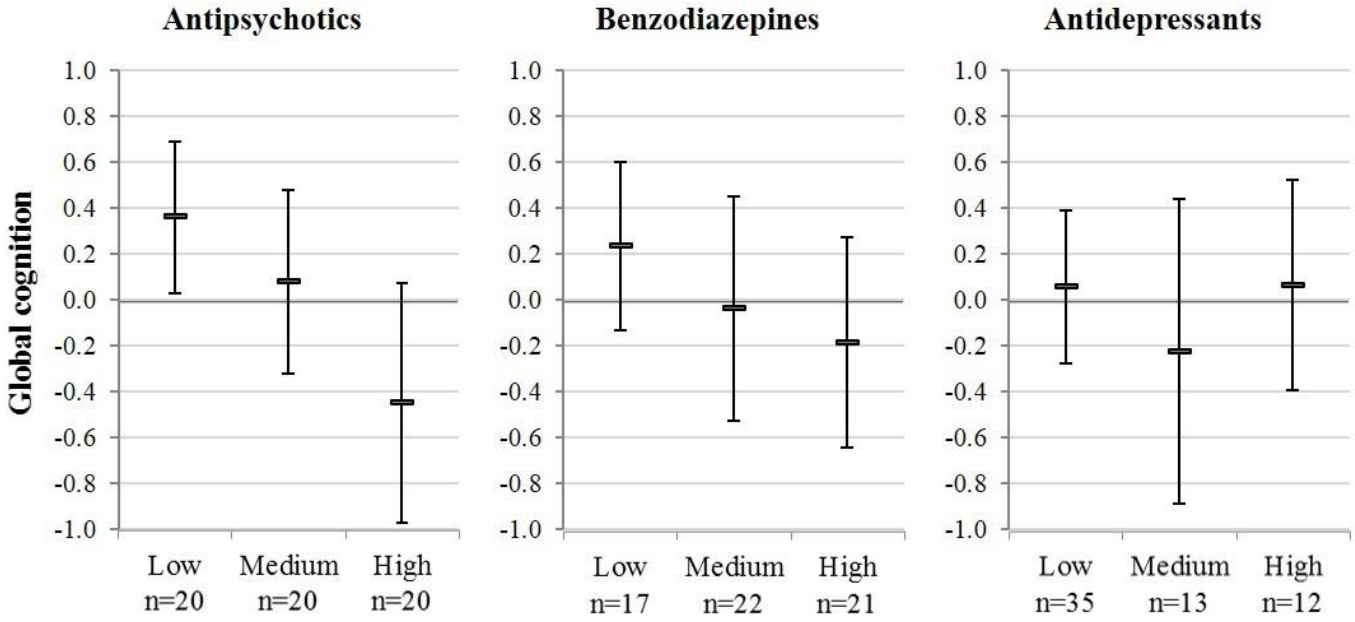

Figure 1 legend: The means and 95% confidence intervals of the cognitive composite score plotted in groups of cumulative DDD years of antipsychotics, benzodiazepines and antidepressants divided based on tertiles to high-, medium- and low-doses. Interpretation: Unadjusted, higher cumulative antipsychotic and benzodiazepine exposure was linearly associated with poorer cognition, but both low and high cumulative antidepressant doses were associated with better cognition than medium doses.

Table 1. Descriptions of the psychiatric medication variables

Name of the variable	Description of the variable
Lifetime cumulative dose	
Lifetime DDD years of benzodiazepines	A sum of DDDs of benzodiazepine medications the person had used, divided by 365.25 days, i.e. exposure to medication that corresponds using one defined daily dose per day for a year.
Lifetime DDD years of antidepressants	A sum of DDDs of antidepressant medications the person had used, divided by 365.25 days.
Lifetime DDD years of antipsychotics	A sum of DDDs of antipsychotic medications the person had used, divided by 365.25 days.
Current psychiatric medication	
Current DDD ratio of benzodiazepines	The daily dose of benzodiazepines the person used at the time of the study divided by their DDD.
Current DDD ratio of antidepressants	The daily dose of antidepressants the person used at the time of the study divided by their DDD.
Current DDD ratio of antipsychotics	The daily dose of antipsychotics the person used at the time of the study divided by their DDD.
Current use of benzodiazepines	Use of benzodiazepines at the time of the study (yes/no).
Current use of antidepressants	Use of antidepressants at the time of the study (yes/no).
Current antipsychotic polypharmacy	Concomitant use of two or more antipsychotic medications at the time of the study (yes/no).
Trends of lifetime use of antipsychotic medication	
Proportion of time with antipsychotic use	Proportion of time during which antipsychotic medication was used of the whole duration of illness[1] classified into three categories[2]: 1) < 50 %, 2) 50 – 95 %, 3) > 95 % of time.
Long antipsychotic-free periods during treatment	Having one or more periods of at least one year without antipsychotic medication since the start of antipsychotic treatment (yes/no), but use of antipsychotics during the cognitive examination.
Being without antipsychotic medication before the cognitive examination	Having a break in antipsychotic medication at least 3 months before and during the cognitive examination (yes/no).
Proportion of time on antipsychotic polypharmacy	Proportion of time with concomitant use of two or more antipsychotic medications of the entire time during which antipsychotic medication was used classified into three classes[2]: 1) <5 %, 2) 5-40 %, 3) >40 % of time.

DDD= defined daily dose, the average maintenance dose based on global health statistic evaluated by WHO [40], DDD ratio= used daily dose divided by defined daily dose; DDD year= exposure to medication that corresponds using one defined daily dose per day for a year. [1]Duration of illness=time since the onset of illness or first psychiatric medication. [2]The classes were chosen based on distribution of the data.

Table 2. Characteristics of the sample

	Schizophrenia
Sociodemographic factors	
Sex, n (%)	
Males	33 (55%)
Education, n (%)[1]	
Low	33 (56%)
Middle	15 (25%)
High	11 (19%)
Occupational status, n (%)	
working	18 (30%)
on disability pension	35 (58%)
Marital status, n (%)	
married/cohabiting	18 (30%)
Clinical factors	
Current use of alcohol (g/day), median (IQR)[1]	1.2 (0-14.0)
Alcohol abuse dg, n (%)[1]	
Yes	6 (10%)
SOFAS, mean (SD)	50.7 (16.8)
Onset age (years), mean (SD)	26.6 (6.3)
Number of hospital treatment days, median (IQR)	210 (84-687)
Psychiatric treatment status, n (%)	
no treatment contact	26 (43%)
non-regular outpatient treatment	7 (12%)
regular outpatient treatment	22 (37%)
inpatient/institution	5 (8%)
Diagnosis, n (%)	
schizophrenia	50 (83%)
schizophreniform disorder	2 (3%)
schizoaffective disorder	6 (10%)
delusional disorder	2 (3%)
Symptom severity	
CGI, mean (SD)	4.5 (1.4)
PANSS, mean (SD)[1]	66.6 (23.5)
Remission, n (%)[1]	
yes	16 (28%)

SOFAS = Social and Occupational Functioning Assessment Scale, CGI = Clinical Global Impression, PANSS = Positive and Negative Syndrome Scale, IQR = interquartile range. Psychiatric treatment status: non-regular outpatient treatment = contact less than once per month or of unknown frequency, regular outpatient treatment = 1-4 times per month and inpatient/institution = being in psychiatric hospital treatment or sheltered home. [1]There were missing data for 1 case in education, 1 case in current use of alcohol, 2 cases in PANSS, 2 cases in remission.

Table 3. Lifetime use and current use of psychiatric medications at 43 years of age in schizophrenia (n=60).

Medication groups	Lifetime use		Current use	
	n (%)	DDD years, Md (IQR)[1]	n (%)	DDD ratio, Md (IQR)[1]
Any antipsychotic medication	59 (98%)	10.4 (5.0-29.7)	51 (85%)	1.2 (0.7-2.5)
Benzodiazepines	43 (72%)	4.6 (1.2-16.1)	23 (38%)	1.0 (0.4-1.5)
Antidepressants	25 (42%)	3.4 (0.8-12.9)	13 (22%)	1.3 (1.0-1.8)

[1]Md=median and IQR=interquartile range were calculated for those with lifetime or current use of the specific medication, not for all cases.

Table 4. The association between lifetime and current benzodiazepine and antidepressant medications and the cognitive composite score in schizophrenia at 43 years of age in linear regression analyses.

	Model[1]			Model[2]		
	B (SE)[1]	Beta[1]	Sig[1]	B (SE)[2]	Beta[2]	Sig[2]
Lifetime DDD years of benzodiazepines[3]	-0.16 (0.14)	-0.18	0.278	-0.05 (0.15)	-0.05	0.754
Lifetime DDD years of antidepressants[3]	0.08 (0.21)	0.09	0.689	0.06 (0.20)	0.06	0.772
Current DDD ratio of benzodiazepines[3]	-0.37 (0.24)	-0.41	0.115	-0.25 (0.21)	-0.27	0.238
Current DDD ratio of antidepressants[3]	-0.60 (0.42)	-0.32	0.148	-0.78 (0.45)	-0.42	0.081
Current use of benzodiazepines	-0.15 (0.27)	-0.07	0.571	0.08 (0.26)	0.04	0.761
Current use of antidepressants	0.48 (0.31)	0.20	0.127	0.19 (0.33)	0.08	0.561

B=unstandardised regression coefficient, SE=standard error, Beta=standardised regression coefficient, Sig=statistical significance. [1]Unadjusted model. [2]Adjusted for gender and onset age. [3]The analyses were completed in a group of those cases that had used the medication and those with no use were excluded.

Table 5. The association between lifetime and current antipsychotic medication variables and cognitive composite score in schizophrenia at 43 years of age in linear regression analyses.

	Model[1]			Model[2]			Model[3]			Model[4]		
	B (SE)[1]	Beta[1]	Sig[1]	B (SE)[2]	Beta[2]	Sig[2]	B (SE)[3]	Beta[3]	Sig[3]	B (SE)[4]	Beta[4]	Sig[4]
Lifetime DDD years of antipsychotics	**-0.37 (0.11)**	**-0.42**	**<0.001**	**-0.28 (0.12)**	**-0.32**	**0.018**	**-0.34 (0.15)**	**-0.39**	**0.020**	-0.24 (0.13)	-0.28	0.066
Proportion of time with antipsychotic use	**-0.34 (0.17)**	**-0.25**	**0.046**	-0.32 (0.16)	-0.23	0.051	-0.31 (0.17)	-0.23	0.066	-0.28 (0.17)	-0.20	0.107
Long antipsychotic-free periods during treatment	-0.07 (0.28)	-0.03	0.809	0.10 (0.27)	0.05	0.722	0.12 (0.27)	0.06	0.653	0.11 (0.28)	0.05	0.689
Being without antipsychotic medication before the cognitive examination	**0.89 (0.35)**	**0.32**	**0.012**	**0.90 (0.33)**	**0.32**	**0.006**	**0.98 (0.36)**	**0.35**	**0.007**	**0.81 (0.35)**	**0.29**	**0.021**
Proportion of time on antipsychotic polypharmacy	**-0.35 (0.16)**	**-0.28**	**0.029**	-0.24 (0.16)	-0.19	0.121	-0.24 (0.18)	-0.19	0.173	-0.20 (0.17)	-0.16	0.235
Current DDD ratio of antipsychotics	**-0.23 (0.10)**	**-0.30**	**0.017**	-0.14 (0.10)	-0.18	0.181	-0.13 (0.11)	-0.17	0.258	-0.12 (0.10)	-0.15	0.251
Current antipsychotic polypharmacy	**-0.74 (0.30)**	**-0.31**	**0.012**	-0.49 (0.31)	-0.21	0.110	-0.47 (0.33)	-0.20	0.152	-0.42 (0.33)	-0.18	0.202

B=unstandardised regression coefficient, SE=standard error, Beta=standardised regression coefficient, Sig=statistical significance. Statistically significant results in **bold**. [1]Unadjusted model. [2]Adjusted for gender and onset age. [3]Adjusted for gender, onset age and logarithmic transformation of cumulative lifetime hospital treatment days. [4]Adjusted for gender, onset age and PANSS positive symptoms.

When adjusted, in addition to gender and onset age, for other covariates (one per model) in separate models:
Being without antipsychotic medication before the cognitive examination was significantly associated with cognition additionally when adjusted with remission (B=0.82, SE=0.36, Beta=0.29, Sig=0.025), educational level (B=0.92, SE=0.33, Beta=0.33, Sig=0.005), current benzodiazepine use (B=0.91, SE=0.33, Beta=0.32, Sig=0.006), current antidepressant use (B=0.90, SE=0.33, Beta=0.32, Sig=0.006) and PANSS negative symptoms (B=0.67, SE=0.34, Beta=0.24, Sig=0.046).

The association between *being without antipsychotic medication before the cognitive examination* and cognition was not significant only, when adjusted in addition to gender and onset age for PANSS disorganisation symptoms (B=0.39, SE=0.31, Beta=0.14, Sig=0.215).

Lifetime DDD years of any antipsychotics was significantly associated with cognition also when adjusted for educational level (B=-0.29, SE=0.12, Beta=-0.33, Sig=0.017), current benzodiazepine use (B=-0.29, SE=0.12, Beta=-0.33, Sig=0.016) or current antidepressant use (B=-0.29, SE=0.12, Beta=-0.33, Sig=0.015).

There were no other significant associations between the other antipsychotic medication variables and cognition in the models described before.

Supplementary material, Methods

Background variables and covariates

Age of illness onset, defined as the age when the first evident psychotic symptoms emerged, was ascertained from medical records.

Level of education was based on questionnaire information gained in the 43-year study on the level of basic education (O level, 9 years or A level, 12 years) and vocational education (none, course or school, currently studying, college, polytechnic or university) which were combined and classified into three categories: low = O level with low vocational education (none, course or school or currently studying), middle = O level with high vocational education (college, polytechnic or university) or A level with low vocational education and high = A level with high vocational education.

Occupational status at the time of the 43-year study was classified into three categories: 1) working, if the subjects were studying, on maternity leave or in full-time or part-time work, 2) on disability pension, if they were retired because of psychiatric or other illness or 3) not working, if they were unemployed, or outside of working life for other reasons. Information was ascertained in an interview in the 43-years study and missing information was completed with Finnish Centre for Pension registers data.

Alcohol abuse diagnosis included subjects with an earlier or current diagnosis of either alcohol abuse or dependency evaluated in the SCID I interview at the 43-year study.

PANSS (Positive and Negative Syndrome Scale) [1] *scores* were evaluated in a PANSS specific interview at the 43-years study. PANSS total symptoms were measured from one week before the interview and divided into positive, negative and disorganisation symptoms based on the model described by van der Gaag et al. [2]. PANSS was also utilised in determining remission status (more below).

The Severity of Illness subscale of the CGI (Clinical Global Impression) [3], ranging from 1 (not ill at all) to 7 (among the most extremely ill), was ascertained in the interview at the 43-year study.

Cumulative number of hospital treatment days was obtained from the Care Register for Health Care (formerly Finnish Hospital Discharge Register).

Psychiatric treatment status was ascertained in the interview at the 43-year study by asking about previous and current psychiatric treatment contacts (place and time of starting the contact, frequency of visits) and grouped to four categories: no treatment contact, non-regular outpatient treatment (less frequent than once per month or of unknown frequency), regular outpatient treatment (visits in the psychiatric services or outpatient rehabilitation group at least once and mostly 1-4 times per month), and inpatient/institution (psychiatric hospital treatment or living in a sheltered home).

Remission, according to the Andreasen symptomatic criteria [4], was defined as having no symptoms (PANSS) at the time of the 43-year study and no psychiatric hospital treatments in 6 months before the study.

Supplementary Table 1. Lifetime use and current use of psychiatric medications at 43 years of age in schizophrenia (n=60).

ATC code	Generic name	Lifetime use		Current use	
		n (%)	DDD years, mean (Sd)	n (%)	DDD, mean (Sd)
Antipsychotic medication		59 (98%)	18.2 (20.2)	51 (85%)	1.6 (1.3)
Typical antipsychotics		54 (90%)	9.9 (14.0)	19 (32%)	0.7 (0.8)
N05AA01	Chlorpromazine	22 (37%)	2.4 (5.8)	-	-
N05AA02	Levomepromazine	26 (43%)	0.9 (2.1)	4 (7%)	0.4 (0.3)
N05AA03	Promazine	20 (33%)	0.5 (0.9)	1 (2%)	0.7
N05AB01	Dixyrazine	1 (2%)	0.01	-	-
N05AB02	Fluphenazine	2 (3%)	20.1 (28.5)	-	-
N05AB03	Perphenazine	36 (60%)	1.4 (2.1)	6 (10%)	0.6 (0.4)
N05AB08	Thioproperazine	1 (2%)	4.3	-	-
N05AC01	Periciazine	1 (2%)	0.04	-	-
N05AC02	Thioridazine	38 (63%)	4.2 (6.3)	1 (2%)	0.7
N05AC04	Pipotiazine	3 (5%)	2.6 (3.8)	-	-
N05AD01	Haloperidol	40 (67%)	2.4 (3.9)	2 (3%)	0.5 (0.07)
N05AD03	Melperone	3 (5%)	0.03 (0.04)	-	-
N05AF01	Flupentixol	4 (7%)	0.4 (0.4)	-	-
N05AF03	Chlorprothixene	15 (25%)	1.1 (1.7)	4 (7%)	0.5 (0.2)
N05AF05	Zuclopenthixol	21 (35%)	3.2 (5.6)	3 (5%)	1.5 (0.9)
N05AG02	Pimozide	1 (2%)	0.4	-	-
N05AL01	Sulpiride	7 (12%)	0.1 (0.1)	-	-
N05AL04	Remoxipride	2 (3%)	0.1 (0.006)	-	-
Atypical antipsychotics		49 (82%)	11.0 (9.9)	43 (72%)	1.6 (0.9)
N05AE03	Sertindole	3 (5%)	0.4 (0.4)	-	-
N05AE04	Ziprasidone	1 (2%)	0.06	-	-
N05AH02	Clozapine	16 (27%)	12.1 (13.3)	11 (18%)	1.4 (0.4)
N05AH03	Olanzapine	31 (52%)	6.7 (7.6)	20 (33%)	1.7 (0.9)
N05AH04	Quetiapine	19 (32%)	2.3 (3.9)	7 (12%)	1.1 (0.9)
N05AH05	Asenapine	1 (2%)	0.03	-	-
N05AX08	Risperidone	36 (60%)	2.2 (3.7)	4 (7%)	0.9 (0.5)
N05AX12	Aripiprazole	11 (18%)	1.1 (1.2)	7 (12%)	0.9 (0.8)
Benzodiazepines		43 (72%)	8.9 (10.2)	23 (38%)	1.2 (1.1)
N03AE01	Clonazepam	9 (15%)	2.3 (3.2)	3 (5%)	0.6 (0.8)
N05BA01	Diazepam	37 (62%)	3.7 (5.2)	8 (13%)	0.9 (0.9)
N05BA02	Chlordiazepoxide	9 (15%)	2.2 (5.2)	1 (2%)	0.8
N05BA04	Oxazepam	27 (45%)	1.7 (3.4)	5 (8%)	0.4 (0.3)
N05BA05	Potassium clorazepate	9 (15%)	1.1 (1.6)	-	-
N05BA06	Lorazepam	13 (22%)	0.8 (0.6)	4 (7%)	1.3 (0.8)
N05BA12	Alprazolam	4 (7%)	0.3 (0.2)	-	-
N05CD02	Nitrazepam	7 (12%)	0.6 (0.9)	-	-
N05CD05	Triazolam	3 (5%)	0.6 (0.7)	-	-
N05CD07	Temazepam	34 (57%)	2.4 (3.6)	7 (12%)	0.9 (0.5)
N05CD08	Midazolam	4 (7%)	0.009 (0.009)	-	-
N05CF01	Zopiclone	25 (42%)	1.8 (3.2)	5 (8%)	0.7 (0.3)
N05CF02	Zolpidem	5 (8%)	1.0 (0.9)	-	-
Antidepressants		25 (42%)	6.9 (6.7)	13 (22%)	1.3 (0.5)
N06AA04	Clomipramine	1 (2%)	0.008	-	-
N06AA09	Amitriptyline	10 (17%)	2.2 (3.1)	3 (5%)	0.9 (0.7)
N06AA10	Nortriptyline	1 (2%)	0.007	1 (2%)	0.07

N06AA12	Doxepin	3 (5%)	0.1 (0.2)	1 (2%)	0.06
N06AA21	Maprotiline	1 (2%)	0.6	-	-
N06AB03	Fluoxetine	9 (15%)	3.5 (4.7)	3 (5%)	1.3 (0.6)
N06AB04	Citalopram	13 (22%)	4.1 (5.8)	2 (3%)	1.1 (0.2)
N06AB05	Paroxetine	4 (7%)	7.0 (4.6)	1 (2%)	2.0
N06AB06	Sertraline	5 (8%)	3.4 (3.2)	1 (2%)	2.0
N06AB08	Fluvoxamine	1 (2%)	0.5	-	-
N06AB10	Escitalopram	1 (2%)	1.0	1 (2%)	1.0
N06AG02	Moclobemide	1 (2%)	0.004	-	-
N06AX03	Mianserin	2 (3%)	1.4 (1.9)	-	-
N06AX11	Mirtazapine	4 (7%)	3.2 (3.9)	2 (3%)	1.0 (0.7)
N06AX16	Venlafaxine	1 (2%)	2.0	1 (2%)	0.8
N06AX17	Milnacipran	1 (2%)	0.09	-	-
Anticholinergic agents					
N04AA02	Biperiden	26 (43%)	1.4 (2.7)	-	-
Other medications					
G02CB01	Bromocriptine	1 (2%)	0.01	-	-
N03AB02	Phenytoin	2 (3%)	6.9 (8.5)	-	-
N03AF01	Carbamazepine	5 (8%)	2.9 (4.3)	1 (2%)	0.07
N03AF02	Oxcarbazepine	1 (2%)	0.06	-	-
N03AG01	Valproic acid	10 (17%)	6.3 (5.8)	10 (17%)	0.8 (0.4)
N03AX09	Lamotrigine	3 (5%)	0.5 (0.9)	1 (2%)	0.7
N03AX11	Topiramate	1 (2%)	1.4	-	-
N03AX14	Levetiracetam	1 (2%)	0.01	-	-
N03AX16	Pregabalin	1 (2%)	0.03	-	-
N04BC05	Pramipexole	1 (2%)	0.02	-	-
N05BB01	Hydroxyzine	8 (13%)	0.3 (0.4)	1 (2%)	1.3
N05CC01	Chloral hydrate	1 (2%)	0.002	-	-
N05CH01	Melatonin	2 (3%)	0.9 (1.2)	2 (3%)	1.5 (0.7)
R06AD02	Promethazine	1 (2%)	0.003	-	-

Means and standard deviations (Sd) are calculated for those who have used the specific medication.

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