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MAJOR ARTICLE

Anticholinergic and Sedative Medications Are Associated With Neurocognitive Performance of Well Treated People With Human Immunodeficiency Virus

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Background. We previously showed that anticholinergic (ACH) medications contribute to self-reported neurocognitive impairment (NCI) in elderly people with human immunodeficiency virus (PWH). The current cross-sectional study further evaluated the effect of ACH and sedative drugs on neurocognitive function in PWH who underwent comprehensive neuropsychological evaluation.

Methods. A medication review was performed in PWH enrolled in the prospective Neurocognitive Assessment in Metabolic and Aging Cohort within the Swiss HIV Cohort Study. Neurocognitive functions were analyzed in 5 domains (motor skills, speed of information, attention/working memory, executive functions, and verbal learning memory). The effect of ACH and sedative medications on neurocognitive functioning was evaluated using linear regression models for the continuous (mean z-score) outcome and multivariable logistic regression models for the binary (presence/absence) outcome.

Results. A total of 963 PWH (80% male, 92% Caucasian, 96% virologically suppressed, median age 52) were included. Fourteen percent of participants were prescribed ≥1 ACH medication and 9% were prescribed ≥1 sedative medication. Overall, 40% of participants had NCI. Sedative medication use was associated with impaired attention/verbal learning and ACH medication use with motor skills deficits both in the continuous (mean z-score difference −0.26 to −0.14, $P < .001$ and $P = .06$) and binary (odds ratio [OR], ≥1.67; $P < .05$) models. Their combined use was associated with deficits in overall neurocognitive functions in both models (mean z-score difference −0.12, $P = .002$ and OR = 1.54, $P = .03$). These associations were unchanged in a subgroup analysis of participants without depression ($n = 824$).

Conclusions. Anticholinergic and sedative medications contribute to NCI. Clinicians need to consider these drugs when assessing NCI in PWH.

Keywords. anticholinergic medication; HIV; neurocognitive impairment; neuro-HIV; sedative medication.

Neurocognitive impairment (NCI) remains a problem in people with human immunodeficiency virus (PWH) despite advances in antiretroviral therapies [1]. Although severe NCI has declined in PWH [2], milder forms of NCI remain common in all PWH, including patients <65 years of age [1, 3], with increased risk of accelerated neurocognitive decline compared with human immunodeficiency virus (HIV)-negative patients [4]. Several risk factors have been identified in PWH including age, female sex, duration of HIV infection, low nadir CD4 cell count, persistent viremia and ongoing inflammatory response, education level, depression, history of central nervous system

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(CNS) infection, increased cardiovascular risk, alcohol binge, unemployment, and neurotoxicity of antiretroviral therapy [5–15]. Mechanisms for antiretroviral neurotoxicity include both indirect (such as vascular mechanisms) and direct mechanisms (such as mitochondrial toxicity, oxidative stress, proinflammatory cytokines, and production of neurotoxic metabolites). Other putative mechanisms include amyloid deposition, damage to small cerebral vessels, or impairment in neurotransmission [16]. Neurocognitive impairment can impact patients' quality of life, medication adherence and the related viral suppression, and life expectancy [17–19].

Medications with anticholinergic (ACH) activity have been associated with dementia in the elderly general population [20]. Furthermore, a high ACH burden has been associated with smaller brain volumes and poorer whiter matter structural integrity, and these effects were shown to be more widespread in PWH compared to the general population suggesting that PWH may be more susceptible to ACH medications neurocognitive effects [21]. Many commonly used medications by PWH have ACH activity (eg, antidepressants, antipsychotics, antihistamines). It was recently reported that use of ACH medication is higher in PWH compared to the general population [21] and that polypharmacy is associated with an increased risk of ACH medication use [22]. Anticholinergic medication use is a potentially modifiable risk factor that should be evaluated in this high-risk population.

We previously described ACH medication use in PWH ≥65 years old in the Swiss HIV Cohort Study (SHCS) and the association with self-reported NCI using 3 cognitive screening questions addressing memory, attention, and reasoning difficulties [22]. The current study aimed to further evaluate the effect of ACH and sedative medications on neurocognitive functions in the Neurocognitive Assessment in the Metabolic and Aging Cohort (NAMACO) study group who underwent comprehensive neuropsychological (NP) evaluation using a standardized assessment battery as part of the NAMACO study.

METHODS

Study Population and Study Design

The NAMACO study is a prospective, longitudinal, multicenter and multilingual study of well treated PWH within the SHCS. The NAMACO study was established to evaluate the impact of HIV infection on the neurocognitive function in an aging HIV-infected population. Study methods have been previously described [23, 24]. In brief, SHCS participants were eligible for NAMACO inclusion if they had a diagnosis of HIV, were aged ≥45 years, and had sufficient oral fluency to undergo a thorough NP evaluation. The NAMACO participants were enrolled regardless of their cognitive complaints between May 1, 2013 and November 30, 2016. The current study was a cross-sectional analysis of the effect of ACH and sedative medications on neurocognitive functions at enrolment in the NAMACO cohort.

Patient Consent Statement

The ethics committee of each hospital center (Ethikkommission Nordwest- und Zentralschweiz EKNZ in Basel, Kantonale Ethikkommission Bern in Bern, Commission Cantonal d'Ethique de la Recherche sur l'être humain in Geneva, Commission Cantonale d'Ethique de la Recherche sur l'être Humain in Lausanne, Ethikkommission Tessin in Lugano, Ethikkommission Ostschweiz [EKOS] in St. Gallen, and Ethikkommission Zürich in Zürich) approved the NAMACO study protocol. All participants signed informed consent before being included.

Neuropsychological Evaluation

Neurocognitive function was evaluated by a neuropsychologist or neurologist trained in behavioral neurology and working under the supervision of a neuropsychologist. Participants completed several tests to assess 5 cognitive domains known to be affected in PWH based on the International Network for Strategic Initiatives in Global HIV trial (INSIGHT) and Strategic Timing of Antiretroviral Treatment (START) [25]. The evaluated domains included motor skills, speed of information processing, attention and working memory, executive functions, and verbal episodic memory. Specific tests to evaluate each domain have been described previously [23, 24]. Raw scores for each NP test were converted to demographically adjusted standard scores (or z-scores). Higher z-scores indicate better neurocognitive performance, conversely lower z-scores reflect worse function.

The Lawton's Instrumental Activities of Daily Living ([IADL] 8 items) were considered regardless of sex. Items that a person did not do before the evaluation were not considered as being changed and were attributed 1 point), and the Patient's Assessment of Own Functioning Inventory (PAOFI) questionnaire (3 items) was used to quantify the impact of NCI on daily functioning [26]. Functional impairment was defined as difficulties reported in at least 2 of 11 items.

Neurocognitive impairment was analyzed as a continuous variable using z-scores and as a categorical variable using the Frascati criteria [27]. Based on the Frascati criteria, participants were categorized as follows: no NCI, asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), HIV-associated dementia (HAD), and non-HIV associated NCI (ie, confounding conditions such as psychiatric disorders (including depression assessed using the Centre for Epidemiological Studies Depression Scale [CES-D], substance use, antiretroviral toxicity, CNS opportunistic infection, stroke or trauma, and neurodegenerative disorders). Asymptomatic neurocognitive impairment and MND were defined as ≥1

standard deviation (SD) below the mean in ≥2 cognitive domains, without (ANI) and with (MND) functional impairment. Human immunodeficiency virus-associated dementia was defined as ≥2 SD below the mean in ≥2 cognitive domains with functional impairment.

Medication Review

A review of the current medication at the time of the NP examination was performed for all participants. Anticholinergic medications were identified using a previously developed ACH scale [22]. Anticholinergic activity was scored 1 to 3, with a higher score indicating more ACH activity (ACH scores of medications are detailed in [22]). Medications with known sedative properties (ie, opioids, muscle relaxants, anticonvulsants, antihistamines, antidepressants, and sedatives) were also identified. A list of medications with sedative properties can be found in the Supplementary Table 1.

Data Collection

Other data collected at the time of the NP examination included demographics, education, comorbidities, duration of known HIV infection, HIV viral load and CD4 cell count within 6 months of NP evaluation, nadir CD4, employment, alcohol binge, substance use, and HIV medications.

Statistical Analysis

Descriptive analyses are presented as median and interquartile range (IQR) for continuous variables and as percentages for categorical variables. The χ^2 test was used to compare participants' characteristics according to the use of sedative and ACH medications and to analyze associations between 2 categorical variables. The effect of medications on the cognitive function was evaluated using linear regression models for the continuous outcome and multivariable logistic regression models for the binary outcome. For the continuous model, NCI was considered as a continuous variable using the mean of the z-scores of the NP tests used. Overall neurocognitive functions considered the mean of the z-scores means of the 5 cognitive domains. For the categorical model, NCI was classified as no impairment versus impairment (ie, presence of ANI, MND, HAD, or other non-HIV NCI). Tested medication groups included the following: (1) ACH drugs (ACH ≥1 = being on at least 1 ACH drug); (2) sedative drugs (being on at least 1 drug with sedative properties); (3) ACH + sedative drugs. The effect of medications on neurocognitive impairment was assessed for each medication group for each individual cognitive domain and for the overall neurocognitive functions. Models were adjusted for patient demographics, known HIV infection duration, HIV acquisition mode, CD4 cell count (nadir), comorbidities, cigarette smoking, history of opportunistic CNS infection, depression, employment, level of education, alcohol binge, current use of illicit substances, duration of HIV treatment, and efavirenz or dolutegravir use. Sensitivity analyses were performed using the continuous model to evaluate whether the effect of medications on cognitive function differed according to gender and the presence or absence of depression. $P < .05$ were considered statistically significant. Statistical analyses were conducted using STATA (StataCorp, College Station, TX).

RESULTS

Study Population

Overall, 981 PWH have been enrolled in the NAMACO cohort; however, 18 had missing data in the NP assessments so a total of 963 PWH were included in the study. Table 1 describes patient characteristics. Overall, participants were male ($n = 769$, 80%) and Caucasian ($n = 883$, 92%), with a median age of 52 (IQR, 49–59) years. Most study participants were receiving antiretroviral treatment ($n = 950$, 99%) and were virologically suppressed (HIV ribonucleic acid <50 copies/mL) ($n = 924$, 96%). Clinical diagnosis of depression was made in 139 (14%) participants. More than half of the study population was employed ($n = 616$, 64%).

Medication Use

A total of 117 participants (12%) met criteria for polypharmacy (≥5 non-HIV medications); the median number of non-HIV drugs was 2 (IQR, 1–4). Overall, the use of ACH and sedative medications was low in this population; 133 (14%) participants were prescribed ≥1 ACH medication (regardless of ACH score), 88 (9%) participants were prescribed ≥1 sedative medication, and 63 (7%) were prescribed ACH plus sedative medications. The most commonly prescribed medications with sedative activity ($n = 194$) included zolpidem ($n = 36$), lorazepam ($n = 27$), and methadone ($n = 27$). Prescriptions for medications with ACH activity ($n = 159$) were most commonly written for escitalopram ($n = 18$), mirtazapine ($n = 16$), and citalopram ($n = 11$) (Table 2). Not surprisingly, individuals who were prescribed ACH drugs were more likely to have a diagnosis of depression ($P < .001$). The majority (82%) of medications with ACH properties that were prescribed to participants had an ACH score of 1 (low ACH burden). The average total ACH score was 1.5 (SD ± 0.9) in patients prescribed ≥1 ACH medication. Both ACH and sedative medication use was higher in females ($P < .01$ and $P < .001$, respectively). Increased age was not associated with ACH or sedative medication use. However, polypharmacy was associated with both ACH and sedative medication use (both $P < .001$).

Neuropsychological Evaluation of the Study Population

Overall, 389 (40%) participants had NCI, 27% and 13% of whom were HIV and non-HIV associated, respectively. Neurocognitive impairment was more often observed in

Table 1. Characteristics of the Study Population

Characteristics	Total	With NCI	Without NCI
Median age, years (IQR)	…	53 (49–61)	52 (49–57)
Male sex, *n* (%)	769	277 (36.0)	492 (64.0)
Female sex, *n* (%)	194	112 (57.7)	82 (42.3)
White ethnicity, *n* (%)	883	320 (36.2)	563 (63.8)
Median education, years (IQR)	…	12 (11–14)	13 (12–15)
Employed, *n* (%)	616	192 (31.2)	424 (68.8)
Unemployed, *n* (%)	347	197 (56.8)	150 (43.2)
HIV acquisition mode, *n* (%)	…	…	…
Men who have sex with men	497	144 (29.0)	353 (71.0)
Heterosexual	320	184 (57.5)	136 (42.5)
IDU	115	43 (37.4)	72 (62.6)
Alcohol binge (at least once a month), *n* (%)	61	24 (39.3)	37 (60.7)
Cigarette smoking, *n* (%)	312	123 (39.4)	189 (60.6)
History of previous IDU, *n* (%)	136	55 (40.4)	81 (59.6)
Use of cannabis/cocaine/heroin use (in past 12 months), *n* (%)	123	40 (32.5)	83 (67.5)
Hepatitis B chronic infection, *n* (%)	27	6 (22.2)	21 (77.8)
Hepatitis C coinfection, *n* (%)	167	74 (44.3)	93 (55.7)
History of syphilis, *n* (%)	245	75 (30.6)	170 (69.4)
Diabetes, *n* (%)	60	36 (60.0)	24 (40.0)
Hypertension, *n* (%)	258	124 (48.1)	134 (51.9)
Depression, *n* (%)	139	70 (50.4)	69 (49.7)
Dyslipidemia, *n* (%)	679	285 (42.0)	394 (58.0)
History of opportunistic CNS infection, *n* (%)	43	26 (60.5)	17 (39.5)
Median known HIV infection duration, years (IQR)	…	17 (11–23)	18 (9–24)
HIV VL <50 copies/mL, *n* (%)	924	371 (40.2)	553 (59.9)
Median current CD4 count, cells/μL (IQR)	…	628 (468–805)	637 (468–820)
Median nadir CD4 count, cells/μL (IQR)	…	170 (69–268)	189 (85–271)
On antiretroviral treatment, *n* (%)	950	383 (40.3)	567 (59.7)
Median antiretroviral treatment duration, years (IQR)	…	12 (7–17)	12 (6–18)
On efavirenz, *n* (%)	200	74 (37.0)	126 (63.0)
On dolutegravir, *n* (%)	88	33 (37.5)	55 (62.5)
Median number of non-HIV drugs (IQR)	…	2 (1–5)	2 (1–3)
Polypharmacy (≥5 non-HIV drugs), *n* (%)	117	71 (60.7)	46 (39.3)
On ≥1 ACH drug score 1, *n* (%)	116	64 (55.2)	52 (44.8)
On ≥1 ACH drug score 2, *n* (%)	9	5 (55.6)	4 (44.4)
On ≥1 ACH drug score 3, *n* (%)	20	12 (60.0)	8 (40.0)
On ≥1 drug with sedative properties, *n* (%)	88	41 (46.6)	47 (53.4)

Abbreviations: ACH, anticholinergic; CNS, central nervous system; HIV, human immunodeficiency virus; IDU, injection drug use; IQR, interquartile range; NCI, neurocognitive impairment (based on Frascati criteria); VL, viral load.

Table 2. Most Commonly Prescribed Medications With Anticholinergic and Sedative Activity

ACH Medications (*n* = 159)		Sedative Medications (*n* = 194)	
ACH Score 1	*n* (%)	…	*n* (%)
Escitalopram	18 (11)	Zolpidem	36 (19)
Mirtazapine	16 (10)	Lorazepam	27 (14)
Citalopram	11 (7)	Methadone	27 (14)
Fluoxetine	10 (6)	Lamotrigine	10 (5)
Levocetirizine	9 (6)	Tramadol	9 (5)
Sertraline	9 (6)	Alprazolam	8 (4)
Alprazolam	8 (5)	Oxazepam	8 (4)
Morphine	6 (4)	Pregabalin	7 (4)
Cetirizine	5 (3)	Zopiclone	6 (3)
Duloxetine	5 (3)	Morphine	6 (3)
ACH score 2	*n* (%)	…	…
Quetiapine	5 (3)	…	…
ACH score 3	*n* (%)	…	…
Paroxetine	6 (4)	…	…

Abbreviations: ACH, anticholinergic.

NOTES: ACH score 1 = low anticholinergic burden; ACH score 2 = moderate ACH burden; ACH score 3 = high ACH burden.

women compared to men (57% vs 36%, $P < .001$). Furthermore, individuals presenting with the following factors were more likely to have NCI compared to those without these factors: depression (50% vs 39%, $P = .01$), unemployment (58% vs 31%, $P < .001$), history of opportunistic CNS infection (60% vs 39%, $P = .006$), or polypharmacy (61% vs 38%, $P < .001$). In contrast, there was no difference in the occurrence of NCI based on whether the participants were on an efavirenz ($P = .27$) or dolutegravir ($P = .56$) containing regimen or based on ACH score ($P > .5$).

When analyzing NCI per domain, 394 participants (41%) had motor skills deficits; 317 (33%) had speed of information processing deficits; 311 (32%) had attention/working memory deficits; 235 (24%) had executive function deficits; and 166 (17%) had verbal learning memory deficits. When further categorizing by medication use, participants on sedative and/or ACH medications were more likely to have deficits in the evaluated cognitive domains (Figure 1).

Effect of Medications With Sedative and Anticholinergic Properties on Cognitive Function

In the linear regression model for the continuous outcome, a trend was observed between the use of ACH medication and impairment in motor skills (mean z-score difference −0.14, $P = .06$), whereas the use of sedative medication was significantly associated with deficits in all evaluated domains (mean z-score difference −0.26 to −0.16, $P \leq .05$). Their combined use was associated with the impairment of motor skills, attention, executive functions, and overall neurocognitive functions (mean z-score difference −0.19 to −0.12, $P \leq .04$) (Table 3a).

In the categorical multivariable regression model for the binary outcome, the use of ACH medication was associated with motor skills impairment (odds ratio [OR], 1.69; 95% confidence interval [CI], 1.07–2.69; $P = .03$), and the use of sedative medication was associated with attention deficits (OR, 1.86; 95% CI, 1.19–2.90; $P = .01$) as well as verbal learning memory (OR, 1.67; 95% CI, 1.00–2.78; $P = .05$). Their combined use

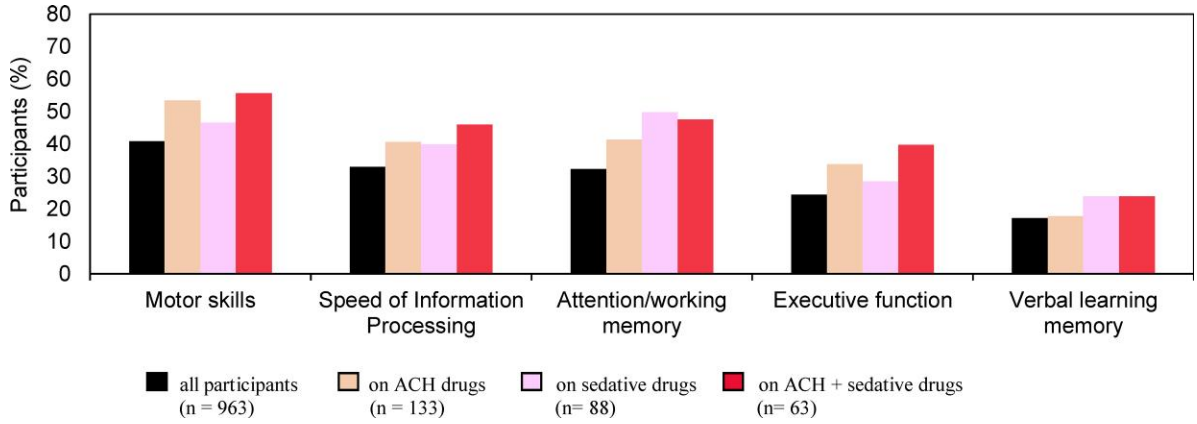

Figure 1. Prevalence of participants with deficits in each individual domain based on anticholinergic (ACH) and sedative medication intake.

significantly impaired the domains of motor skills (OR, 1.62; 95% CI, 1.12–2.34; $P = .01$), attention (OR, 1.65; 95% CI, 1.12–2.41; $P = .01$), and the overall neurocognitive functions (OR, 1.54; 95% CI, 1.05–2.26; $P = .03$), consistent with the continuous model (Table 3b).

Sensitivity Analyses

In the adjusted linear regression model including only women, the use of an ACH medication as well as the combined use of ACH and sedative medications were associated with impairment in motor skills and executive functions (Supplementary Table 2a). The model including only men showed an association between the use of sedative medications and impairment in all cognitive domains. The combined use of ACH and sedative medications was also associated with deficits in all domains with the exception of verbal leaning memory (Supplementary Table 2b).

Another sensitivity analysis was performed to evaluate the effect of ACH and sedative medications in individuals without and with depression, a known confounder for NCI. The medication effects on the cognitive domains were for the most part maintained in the subgroup of individuals without depression ($n = 824$) (Supplementary Table 3a). In contrast, in the subgroup of individuals with depression, the use of ACH medication was associated with improvement in motor skills and overall neurocognitive functions (Supplementary Table 3b).

DISCUSSION

We previously demonstrated that ACH medication use was associated with self-reported NCI (subjective complaints) in PWH ≥65 years in the SHCS [22]. The present study was conducted in a large cohort of both older and middle-aged PWH who underwent comprehensive NP evaluation and confirms that ACH and sedative medications can contribute to NCI, which comprised mostly ANI in our population. The use of ACH medication was associated with impaired motor skills, sedative drugs with attention and verbal learning deficits, and their combined use with impairment of the overall neurocognitive functions. These associations were found both in the continuous and binary models after adjusting for significant confounding factors (ie, depression, unemployment, shorter duration of education, longer antiretroviral treatment, and older age) previously identified in the baseline analysis of the NAMACO cohort [23].

Our findings are not unexpected considering that ACH medications block the neurotransmitter acetylcholine, which plays an important role in the brain and muscle functions including memory, attention, or voluntary movements [28]. Furthermore, sedative drugs (ie, benzodiazepines mostly prescribed in our study) act on the gamma aminobutyric acid (GABA) pathway, which plays an important role in learning, memory, and executive functions [29]. Our observations are in line with studies conducted in middle-aged PWH and that demonstrated an association between ACH medication and poorer executive functions or global cognition [21, 30]. People with HIV on benzodiazepines were also shown to have NCI and poorer processing speed [31]. However, it should be noted that 50% of the study participants were not virologically suppressed in some studies [30, 31], which represents a confounding factor.

Consistent with our previous study in elderly PWH [22], commonly used ACH medications included antidepressants. This observation is not surprising considering that depression is an important driver of NCI [12, 23, 32], which was shown to impact several neurocognitive domains including executive function, speed of information processing, attention and working memory, and verbal episodic memory [33]. One could argue that NCI may be attributed to the depressive state rather than the medications. We demonstrated that ACH and sedative medications remained significantly associated with NCI after excluding participants with depression. In contrast, we observed that individuals with depression improved cognitively while on ACH

Table 3. Effect of Medications with ACH and Sedative Properties on Individual Neurocognitive Domains and Overall Neurocognitive Functions

(a) Continuous Model

… …	Motor Skills			Speed of Information Processing			Attention/Working Memory		
	Coefficient[a]	(95% CI)	*P* Value	Coefficient[a]	(95% CI)	*P* Value	Coefficient[a]	(95% CI)	*P* Value
ACH score ≥1	−.14	(−.30 to .01)	.06	−.01	(−.19 to .16)	.90	.05	(−.10 to .20)	.53
Sedative drug	−.16	(−.30 to −.01)	.03	−.17	(−.33 to −.00)	.05	−.26	(−.40 to −.12)	<.001
ACH + sedative drug	−.19	(−.31 to −.06)	.003	−.10	(−.24 to .04)	.15	−.13	(−.25 to −.01)	.04

… …	Executive Functions			Verbal Learning Memory			Overall Neurocognitive Functions		
	Coefficient[a]	(95% CI)	*P* Value	Coefficient[a]	(95% CI)	*P* Value	Coefficient[a]	(95% CI)	*P* Value
ACH score ≥1	−.03	(−.14 to .08)	.60	.13	(−.02 to .28)	.10	.00	(−.10 to .10)	.98
Sedative drug	−.16	(−.27 to −.06)	.002	−.26	(−.40 to −.12)	<.001	−.20	(−.29 to −.11)	<.001
ACH + sedative drug	−.13	(−.21 to −.04)	.005	−.08	(−.20 to .04)	.22	−.12	(−.20 to −.04)	.002

(b) Binary Model

… …	Motor Skills			Speed of Information Processing			Attention/Working Memory		
	OR[b]	(95% CI)	*P* Value	OR[b]	(95% CI)	*P* Value	OR[b]	(95% CI)	*P* Value
ACH score ≥1	1.69	(1.07–2.69)	.03	.98	(.61–1.59)	.93	1.14	(.70–1.86)	.61
Sedative drug	1.26	(.82–1.95)	.29	1.36	(.87–2.11)	.17	1.86	(1.19–2.90)	.01
ACH + sedative drug	1.62	(1.12–2.34)	.01	1.21	(.83–1.77)	.32	1.65	(1.12–2.41)	.01

… …	Executive Functions			Verbal Learning Memory			Overall Neurocognitive Functions		
	OR[b]	(95% CI)	*P* Value	OR[b]	(95% CI)	*P* Value	OR[b]	(95% CI)	*P* Value
ACH score ≥1	1.10	(.65–1.87)	.71	.83	(.47–1.48)	.53	1.55	(.96–2.52)	.08
Sedative drug	1.29	(.79–2.10)	.30	1.67	(1.00–2.78)	.05	1.33	(.85–2.09)	.21
ACH + sedative drug	1.19	(.78–1.81)	.42	1.24	(.80–1.93)	.33	1.54	(1.05–2.26)	.03

Abbreviations: ACH, anticholinergic; CI, confidence interval; OR, odds ratio.

NOTE: (a) NCI analyzed as a continuous variable (b) as a binary variable (as per Frascati classification).

[a]Adjusted for age, sex, ethnicity, level of education, human immunodeficiency virus (HIV) acquisition mode, alcohol binge, current use of cannabis, cocaine or heroin, history of cardiovascular events, diabetes, hypertension, dyslipidemia, cigarette smoking, history of opportunistic central nervous system (CNS) infection, depression, hepatitis B and C coinfections, syphilis, CD4 cell count, duration of antiretroviral treatment, efavirenz- or dolutegravir-based treatment. Beta-coefficients for the outcomes were shown in the model. For 1-unit increase of predictor variable (eg, ACH score), the outcome variable will increase (+) or decrease (−) by the beta-coefficient (eg, z-score).

[b]Adjusted for age, sex, ethnicity, level of education, HIV acquisition mode, alcohol binge, current use of cannabis, cocaine or heroin, history of cardiovascular events, diabetes, hypertension, dyslipidemia, cigarette smoking, history of opportunistic CNS infection, depression, hepatitis B and C coinfections, syphilis, CD4 cell count, duration of antiretroviral treatment, efavirenz- or dolutegravir-based treatment.

medication (ie, antidepressants with ACH properties), which suggests that treatment of depression has greater benefit on NCI than the risk associated with the antidepressant-related ACH activity. As we previously observed in elderly PWH, we found an association between low-burden ACH medications and NCI, even though the risk of cognitive impairment is generally reported for drugs with a high ACH burden in the general population. This difference has been attributed to the fact that PWH may be more sensitive to the effect of ACH medications compared to the general population [30]. This is particularly important as PWH age. Despite known risks of these medications in the geriatric population, we previously showed that ACH use remains high in elderly PWH [22]. In addition, this population is at increased risk of other comorbidities (eg, osteoporosis) [34], which could exacerbate the deleterious effects of ACH medications (eg, falls resulting in fractures). Evaluation of ACH burden in this population will be particularly important.

In our study, females were more frequently prescribed ACH and sedative medications compared to males. This observation is consistent with a previous SHCS analysis [35] and studies in the general population showing that benzodiazepines or antidepressants are more often prescribed in females compared to males [36]. This gender difference in prescribing has been attributed notably to the fact that women are more likely to seek consultation for mental healthcare [37]. Thus, the higher use of ACH and sedative medications may partly explain our finding that NCI is more prevalent in females. The higher vulnerability of females to cognitive impairment with notably motor skills deficits has been reported in a previous study [38] and is consistent with our observation. The greater vulnerability of females is thought to possibly be related to sociodemographic factors (ie, lower education, poverty, and depression), which can have adverse effects on the brain that lower the cognitive reserve [38].

No significant association was found between increased age and ACH or sedative medication use, which could be explained by the relatively narrow age range of our study population.

This study has several strengths. The analysis included a large number of well treated PWH thereby minimizing confounders

related to detectable viral load. The NP evaluation was performed by trained neuropsychologists in several languages to allow all participants to be evaluated in their preferred language. All medications are systematically documented in the SHCS database and updated at each medical visit; therefore, the analysis was based on a comprehensive list of comedications taken by the participants. Finally, only medications with documented evidence of ACH activity [22] or sedative properties were retained in the analysis, thus enabling a more specific evaluation of their effect on neurocognitive function. Several limitations should be acknowledged. The Frascati criteria were used to identify NCI, which may have led to false-positive NCI due to the large number of neuropsychological tests considered and the assumption that the resulting z-scores follow a normal distribution, thereby increasing the odds of diagnosing NCI by chance, notably ANI. Another disadvantage of the Frascati criteria is that the binary approach (ie, NCI vs no NCI) can miss subtler differences in z-score values. These issues were taken into account by conducting separate analyses based on the Frascati criteria and the mean z-scores. When comparing the 2 analyses, the binary model (presence and absence of NCI as per Frascati classification) proved indeed to be less sensitive than the continuous model (mean z-score) because the associations between sedative medications and deficits in motor skills, speed of information, executive functions, and overall neurocognitive functions were not captured in the binary model. Adherence was only evaluated for HIV drugs; therefore, we could not assess whether participants were taking their ACH or sedative medications as prescribed. We have previously shown that PWH may prioritize their HIV treatment and their comedications in a different manner [39]. Depressive symptoms were assessed using the CES-D score and not by a psychologist or psychiatrist. The CES-D examines depressive symptoms and is not a diagnostic tool for clinical depression, and therefore we cannot exclude an underestimation of the clinical diagnosis of depression. Due to the absence of a control group, it is unknown whether the association between ACH and/or sedative medications and NCI is different in PWH compared to the general population. Furthermore, this study did not distinguish between HIV and non-HIV-related NCI. It may be hypothesized that the latter may have a similar pattern as in the general population. Finally, the ACH and sedative medications dose or duration of use were not accounted for in the analysis.

Longitudinal studies are needed to examine the long-term effects of these medications on cognitive performance but also to evaluate whether switching to medications devoid of ACH or sedative effects improves cognition. Of interest, a worsening of cognitive function over time has been reported in elderly HIV-negative individuals on ACH medications particularly for the executive functions and the episodic memory [40]. Furthermore, the cholinesterase inhibitor rivastigmine, which has an opposite effect compared with ACH medications, was shown to improve psychomotor speed in individuals with HIV-associated neurocognitive disorders [41]. A reduction in the ACH burden in a cohort of middle-aged PWH was also shown to improve executive functions, retention, and overall cognition [21]. The timeline for resolution of NCI may vary depending on the drug. Neurocognitive deficits have been shown to persist for as long as 3 to 4 years after benzodiazepines discontinuation in HIV-negative individuals on long-term treatment with benzodiazepines [42].

CONCLUSIONS

In conclusion, medications with ACH and/or sedative properties contribute to NCI in well treated PWH. Therefore, HIV clinicians need to consider non-HIV medications when evaluating NCI. Anticholinergic and sedative medications are used more often in females, which may explain the higher prevalence of NCI in females compared to males, although this observation could also relate to sociodemographic differences. In future studies, researchers will need to evaluate the impact of discontinuing or substituting ACH and sedative medications on neurocognitive performance particularly in well treated PWH.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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