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POLYPHARMACY IS ASSOCIATED WITH WORSE NEUROCOGNITIVE PERFORMANCE IN AGING ADULTS

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Abstract

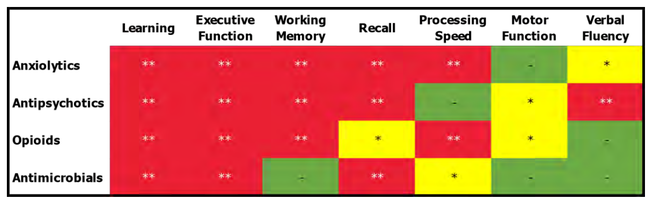
Background: Persons living with HIV (PLWH) have more aging-related diseases, use more prescribed drugs, and are more likely to have neurocognitive (NC) impairment than the general population. Medical and psychiatric comorbidities increase the risk of NC impairment in PLWH but the neurotoxicity of drugs used to treat these diseases remains under-investigated.

Methods: 956 PLWH taking antiretroviral therapy (ART) and enrolled in neuroHIV cohorts underwent NC assessment. Demographically-adjusted T-scores were computed for seven cognitive domains and global performance. The most common classes of concomitant drugs were antidepressants (31%), antimicrobials (26%), non-steroidal anti-inflammatory drugs (21%), opioids (16%), gastric acid drugs (16%), antipsychotics (13%), antihypertensives (11%), and anxiolytics (11%). Polypharmacy was defined as taking at least 5 concomitant drugs. Psychiatric and substance use diagnoses were available for 719 participants. Stepwise multivariable linear regressions using the Akaike Information Criterion modeled NC performance as a function of concomitant medications, adjusting for age, sex, and HIV disease and treatment characteristics.

Results: Participants were generally middle-aged (mean 44) white (53%) men (86%) who had AIDS (56%), viral suppression (72%), and immune recovery (median CD4+ count 488/μL). The mean number of concomitant drugs was 3.3 (range 0-24). Overall, PLWH who took more concomitant drugs had worse global performance (r=0.15, p<0.001), as did those who took ≥ 5 concomitant drugs (d=0.28, p<0.001). Worse global performance was associated with use of anxiolytics (p<0.001), opioids (p=0.008), antimicrobials (p=0.009), and antipsychotics (p=0.03) (Model p<0.001). Concomitant drug classes were most frequently associated with worse executive functioning and learning (see Figure). Accounting for psychiatric, medical, and substance use diagnoses did not significantly weaken the associations between concomitant drugs and global performance.

Conclusions: Concomitant drug use is associated with worse NC performance. Distinguishing the effects of concomitant drugs from those of underlying diseases is complex but our analyses support that certain drug classes may cause neurotoxicity, which could be reversible or irreversible. Different drug classes were associated with different cognitive patterns, suggesting that they differently affect the neurobiological pathways underlying these abilities.

FIGURE 2. SUMMARY OF MULTIVARIATE ANALYSES OF CONCOMITANT DRUG CLASSES WITH NEUROCOGNITIVE PERFORMANCE



** (Red): p < 0.01, * (Yellow): p < 0.05, - (Green): p > 0.10, statistical significance

Introduction

- PLWH have more aging-related diseases, use more prescribed drugs, *e.g.*, polypharmacy[1], and are more likely to have NC impairment.
- Medical and psychiatric comorbidities increase the risk of NC impairment in PLWH[2].
- Evidence of neurotoxicity of antiretroviral therapy (ART) and concomitant drugs has been found, but remains under-investigated[3,4].

Methods

- Data were collected between 1999 and 2018 from participants who enrolled in neuroHIV cohort studies at the University of California, San Diego, including the HIV Neurobehavioral Research Center and the Translational Methamphetamine AIDS Research Center cohorts.
- Key eligibility criteria: Women and men living with HIV disease who were taking combination ART for at least 3 months and had undergone a standardized, comprehensive NC assessment (Table 1).
- The most common classes of concomitant drugs were antidepressants (31%), antimicrobials (26%), non-steroidal anti-inflammatory drugs (21%), opioids (16%), gastric acid drugs (16%), antipsychotics (13%), antihypertensives (11%), and anxiolytics (11%). Polypharmacy was defined as taking ≥5 concomitant drugs[1].
- Demographically adjusted T-scores were derived for 7 cognitive domains and global performance and these T-scores were used to create domain scores.[4] Psychiatric diagnoses, substance use, and other comorbidities were available from 719 participants.
- Stepwise multivariable linear regression modeling was performed using the Akaike Information Criterion.

Table 1. DEMOGRAPHIC DATA OF STUDY PARTICIPANTS IN THE NON-POLYPHARMACY VERSUS POLYPHARMACY GROUP*

Variable		Non-Polypharmacy (n=677)	Polypharmacy (n=279)	p
Age (Years), mean (SD)		42.2 (10.2)	48.9 (10.5)	<0.01
Sex (Male), n (%)		584 (86.4)	242 (86.7)	0.89
Race, n (%)	Asian	12 (2)	2 (1)	
	Black	121 (18)	38 (14)	
	Hispanic	199 (29)	44 (16)	<0.01
	White	322 (48)	186 (66)	
	Other	23 (3)	9 (3)	
CD4+ T-cell Count, mean (SD), ml^{-1}		520 (285)	539 (355)	0.44
Plasma HIV RNA, log mean (SD)		2.363 (0.928)	2.107 (0.844)	<0.01
ART, n (%)	INSTI	109 (16)	71 (25)	
	NNRTI	238 (35)	88 (32)	0.01
	PI	275 (41)	135 (48)	
Comorbidities, n (%)				
Lifetime Substance Use		349/473 (73.8)	185/252 (73.4)	0.91
Lifetime Psychiatric Diagnosis		42/312 (13.5)	36/185 (19.5)	0.08
Diabetes		27/677 (4.0)	39/279 (14.0)	<0.01
Hypertension		113/663 (17.0)	115/279 (41.2)	<0.01

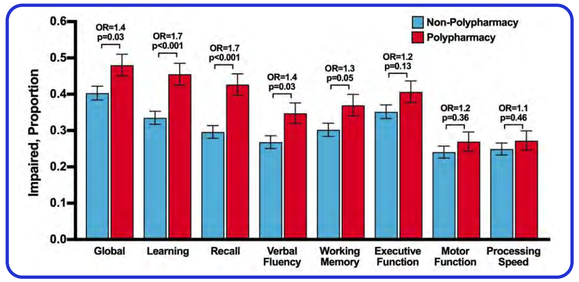
Results

Table 2. COGNITIVE PERFORMANCE BY POLYPHARMACY AND AGE. Values are T-Score Mean (Standard Deviation)

Outcome	Non-Polypharmacy (n=677)	Polypharmacy (n=279)	p	Age<50 (n=649)	**Age≥50** (n=307)	p
Global	46.4 (0.3)	44.5 (0.4)	<0.01	46.5 (0.3)	44.6 (0.4)	<0.01
Executive Functioning	46.6 (0.4)	44.5 (0.5)	<0.01	46.2 (0.3)	45.6 (0.5)	<0.01
Learning	44.3 (0.4)	41.4 (0.5)	<0.01	44.6 (0.4)	41.0 (0.5)	<0.01
Working Memory	45.5 (0.4)	43.5 (0.6)	0.01	44.8 (0.4)	45.2 (0.6)	0.41
Recall	45.5 (0.4)	42.2 (0.6)	<0.01	45.8 (0.4)	41.6 (0.6)	<0.01
Speed of Information Processing	47.6 (0.3)	46.0 (0.5)	0.02	47.6 (0.3)	46.1 (0.5)	<0.01
Motor Functioning	46.5 (0.4)	44.7 (0.6)	0.03	46.7 (0.4)	44.6 (0.6)	<0.01
Verbal Fluency	48.1 (0.3)	46.4 (0.5)	<0.01	47.8 (0.3)	47.1 (0.5)	0.28

- The mean number of concomitant drugs was 3.3 (SD 3.9, range 0-24). The median number of concomitant drugs increased with age, from 1 in < 40 years (n=362), to 2 in 41-50 years (n=321), 3 in 51-60 years (n=204), 6 in 61-70 years (n=63) and 9 in ≥ 71 years (n=6).
- Overall, PLWH who who took more concomitant drugs had worse global performance (r=0.15, p<0.001) as did those who met the definition of polypharmacy (Cohen's d=0.28, p<0.001) (Table 2). Polypharmacy was associated with impaired Learning, Recall, Working Memory, and Verbal Fluency (Figure 1)
- Concomitant drugs associated with NC performance included:
  - Anxiolytics (n=105, 11%): lorazepam, clonazepam, temazepam, alprazolam, diazepam
  - Antipsychotics (n=124, 13%): perphenazine-amitriptyline, quetiapine, risperidone, lamotrigine, olanzapine, aripiprazole, prochlorperazine, or lithium carbonate
  - Opioids (n=153, 16%): hydrocodone, oxycodone, methadone, morphine, codeine, dihydrocodeine or butabital/ASA/CAFF
  - Antimicrobials (n=249, 26%): sulfamethoxazole/trimethoprim, acyclovir, fluconazole, valacyclovir, dapsone, or ganciclovir
- Among ART drug classes, protease inhibitor use was associated with worse global performance
  - No association was present between NC performance and either non-nucleoside reverse transcriptase inhibitor or integrase inhibitor use

FIGURE 1. ASSOCIATION OF ANXIOLYTIC USE AND COGNITIVE PERFORMANCE AS A FUNCTION OF POLYPHARMACY



- Worse global performance was associated with use of Anxiolytics (p<0.001), Opioids (p=0.008), Antimicrobials (p=0.009), Antipsychotics (p=0.03), and Protease inhibitors (p=0.006). Multivariate analysis accounting for comorbid conditions did not significantly weaken the associations (Model p<0.001).
- The pattern of association between concomitant drug classes and NC domain performance varied (Figure 2)
  - Learning, Working Memory, Recall, and Executive Function were most commonly affected.

Conclusions

- This was the first analysis of the impact of concomitant drugs on NC performance in men from multiple neuroHIV cohorts.
- Polypharmacy was common among PLWH (29.2%).
- Concomitant drug use and age were associated with worse NC performance.
- Distinguishing the effects of concomitant drugs from those of underlying diseases is complex but our findings support that certain drug classes may cause neurotoxicity, which may be reversible or irreversible.
- Different drug classes were associated with different cognitive patterns, suggesting that they differently affect the neurobiological pathways underlying these abilities.
- **Polypharmacy might confer a higher risk of NC impairment and have greater negative impact for aging PLWH. Clinicians should consider cognitive evaluation, drug substitution, or regimen simplification.**

Acknowledgments

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