Substance abuse may hasten motor onset of Huntington disease

Evaluating the Enroll-HD database

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ABSTRACT

Objective: To investigate the relationship between substances of abuse and age at motor onset (AMO) in patients with Huntington disease (HD) in a large and diverse patient population.

Methods: This was a retrospective, observational study of the Enroll-HD database. Participants were determined to belong to 1 of 3 substance abuse groups: (1) tobacco abusers, (2) alcohol abusers, and (3) drug abusers. A group of participants who had never abused substances served as a control group. The average AMO of patients in the substance abuse groups was compared to the control group. The number of CAG repeats was used as a covariate in all analyses.

Results: The average difference in AMOs of participants in the tobacco ($n = 566$), alcohol ($n = 374$), and drug abuse groups ($n = 217$) compared to the control group ($n = 692$) were 2.3 ($F_{1, 1,258} = 33.8, p < 0.0001$), 1.0 ($F_{1, 1,066} = 4.2, p = 0.04$), and 3.3 ($F_{1, 909} = 29.7, p < 0.0001$) years earlier, respectively. In all substance abuse groups, the AMO was lowered to a greater degree in female participants than it was in male participants.

Conclusions: Substances of abuse have a strong effect on the AMO in patients with HD. These effects seem to be amplified in women with HD compared to men. These results may provide a safe intervention capable of adding disease-free years to patients with HD. *Neurology*® 2017;88:909-915

GLOSSARY

AMO = age at motor onset; **ANCOVA** = analysis of covariance; **HD** = Huntington disease; **SNP** = single nucleotide polymorphism.

The age at motor onset (AMO) of Huntington disease (HD) is primarily determined by the number of CAG repeats within the *HTT* gene. However, environmental factors also contribute up to one-third of the variance of this age.¹ Substances of abuse may influence the onset and progression of neurodegenerative diseases, including HD. Few studies have directly evaluated this question. Two previous studies found no significant association between drinking and smoking habits and AMO in patients with HD.^{2,3} A more recent study from 2007 showed an association with earlier onset in those who used substances.⁴ The latter study was the largest study of its kind, including 1,976 participants; however, it did not control for CAG repeat length. The most recent study identified a significant association as well as a sex effect where female participants who used substances had an earlier AMO compared to male participants.⁵ This study controlled for CAG repeats, but was conducted in only 133 participants from a single center.

The aim of the current study was to further investigate the relationship between substance abuse and AMO in patients with HD from the Enroll-HD database. Our ability to control for CAG repeat length and evaluate for a sex effect in such a large and diverse population will provide results that may be used to optimize the care and education that patients with HD receive.

METHODS Enroll-HD is a global clinical research platform designed to facilitate clinical research in HD. Core datasets are collected annually on all research participants as part of this multicenter longitudinal observational study of HD. Data are monitored for quality and accuracy using a risk-based monitoring approach.

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The database currently includes 4,146 participants from 139 study sites across the world; participants who have premotor manifest HD or motor manifest HD, genotype-negative participants, and family controls are included. At enrollment into this study, participants answer a comprehensive questionnaire exploring their medical history as well as details about their current social, medical, and family background (figure 1). The questions related to substance abuse are described below and were used to determine how each person was classified based on substance abuse history.

Tobacco. At baseline, participants are asked if they have ever smoked. For those that respond with a yes, they are then asked how many cigarettes per day that they smoked and how many years they smoked. Participants are also asked “Do you currently smoke?” Again, anyone who responds positively is asked how many cigarettes per day he or she smokes and how many years he or she has smoked. A pack-year history is reported for the current and past smoking history questions based on this information. However, the number of cigarettes smoked or the number of years smoked, which is used to calculate these pack-year histories, is not readily available in the dataset.

Alcohol. Participants are asked if they have “had alcohol problems in the past.” They are also asked if they currently drink alcohol, with currently referring to the time of enrollment into the study. For those who confirm current alcohol use, they are then asked to quantify how many units per week they consume. The provided definition of a unit of alcohol is 1 glass of wine (125 mL) or 8 fluid ounces of beer (284 mL) or 1 measure of spirits (25–35 mL).

Drugs. Participants are asked if they have ever abused drugs. Those confirming a history of drug abuse are also asked if they seldom ($\leq$ once per month), occasionally (2–3 times per month), or frequently (more than once weekly) used drugs. Drugs for nonmedical uses are defined as marijuana, heroin, cocaine, club drugs (ecstasy, γ -hydroxybutyrate, roofies), amphetamines, Ritalin, hallucinogens, inhalants, opium, painkillers, barbiturates/sedatives, and tranquilizers. Participants are then asked if they currently use drugs (at the time of enrollment) for nonmedical reasons. Again, those confirming drug use at enrollment are asked what type of drugs they use as well as the frequency of use.

Overview. Participants were divided into 1 of 3 substance abuse groups based on response to the above questions related to substance abuse. The tobacco abuse group included participants who reported both current and past tobacco abuse. The alcohol abuse group included participants who reported that they were consuming ≥ 14 units of alcohol per week at baseline, as well as participants with a reported history of alcohol problems in the past. The lifetime drug abuse group included participants with a history of drug abuse, as well as those who also reported drug abuse at baseline. A control group included participants who did not report either current or past abuse of tobacco, alcohol, or drugs. A more detailed description of these groups and the rationale for the division into these groups is described in the Results. Participants who had an AMO of 21 years or less were excluded from this study ($n = 55$). In general, patients with an AMO of 21 years or less are considered to have juvenile HD, and in this group, the average AMO was 16.7 (SD 4.63) with a range of AMO from 4 to 21 years. It is unlikely that these participants abused substances prior to their AMO; therefore, including them in the analysis may confound the findings.

Previously published studies have hypothesized that substances of abuse may hasten AMO in women more than in men. As

Figure 1 Exclusions

HD = Huntington disease.

a result, the average AMO of men and women was also evaluated separately in each substance abuse group.

Statistical analysis. IBM (Armonk, NY) SPSS Statistics version 23 was used to perform all statistical analyses. Average age at assessment, unadjusted average age at motor onset, average duration of motor illness, and average number of CAG repeats were compared between men and women using independent samples

t tests. Chi-square tests were performed to compare sex difference in the frequency of use of tobacco, alcohol, and drugs in the substance abuse groups compared to the control group.

The relationships between the presence of certain substances of abuse and the effect that they have on AMO were assessed using separate analyses of covariance (ANCOVAs). Sex (when applicable) and CAG repeat number were used as covariates for all ANCOVA analyses and all results are reported as the adjusted AMO. Interaction terms for sex by age at onset effect were entered into the model but were removed if not significant. Results were considered significant if they had a *p* value of <0.05. Effect sizes were calculated for each analysis using Cohen effect size calculation.

Standard protocol approvals, registrations, and patient consents. All sites are required to obtain and maintain local ethics committee approvals. Participants must have signed informed consent forms for their data to be included in the datasets.

RESULTS Demographics. Table 1 contains baseline demographics and disease-related information for the 3 substance abuse groups and the controls. Tobacco was the most commonly abused substance (*n* = 566), followed by alcohol (*n* = 374) and drugs (*n* = 217). The control group included 692 participants.

Table 2 outlines sex differences among all participants. Notable findings from this table include the difference in AMO between men and women (when adjusted for CAG repeat length), with men having a significantly earlier average AMO, regardless of substance abuse status. A difference in AMO based on sex alone has not previously been reported in the literature. Table 2 also outlines the fact that a higher percentage of men than women abused substances and the difference is statistically significant across all substance abuse groups, except for tobacco abuse.

Tobacco abuse decreases the AMO of HD. There were 1,087 participants who reported a medical history significant for tobacco abuse. It is not possible to determine, based on the available information, when participants were smoking relative to their AMO. Therefore, a comparison of the AMO between participants who reported a medical history of tobacco abuse vs those who did not would likely be inaccurate because patients who smoked very occasionally and

quit many years prior to their AMO would be included.

A total of 520 of the 1,086 participants who reported historical tobacco abuse did not report current abuse at baseline assessment, demonstrating a relatively high rate of smoking cessation. The 566 participants who reported current tobacco abuse and historical tobacco abuse comprised the tobacco abuse group described above (figure 2A).

While it is impossible to determine when those participants started smoking, it is unlikely that a significant number of patients began after their AMO. This assumption is strengthened by noting that 99% of cigarette smokers in the United States started smoking by age 26.^{6,7} However, the average AMO of patients in the tobacco abuse group was 42.7 (SD 10.0) years. Also, by excluding participants with an AMO of 21 years or less, the chances of including patients who began to smoke after their AMO is decreased. Despite these assumptions, it is not possible to definitively know when these participants started smoking.

The average AMO of participants in the tobacco abuse group was 2.3 years earlier than that of controls, suggesting that smoking can significantly affect the AMO in HD (effect size 0.40). This effect was stronger in female than in male participants. Among female participants, the AMO was 2.7 years earlier among tobacco abusers compared to controls (effect size 0.37), while male smokers had an AMO that was 2.0 years earlier than controls (effect size 0.29). These results are outlined in table 3.

Alcohol abuse decreases the AMO of HD. Unlike the questions related to tobacco abuse, there is a discontinuity between past and current history of alcohol abuse in the Enroll-HD database. Regarding their medical history, patients are asked if they have had an “alcohol problem” in the past, a question requiring each patient to make a subjective judgment of drinking behavior. Conversely, the question about alcohol use at the time of enrollment asks the patient to quantify current alcohol use, providing more objective information on the patient’s current behavior.

Table 1 Baseline demographics

	Tobacco abusers	Alcohol abusers	Drug abusers	Control group
No.	566	374	217	692
Average age at assessment, y	49.1 ± 10.7 ^a	53.3 ± 11.1 ^a	48.5 ± 11.0 ^a	54.17 ± 12.3
Unadjusted average age at onset, y	42.7 ± 10.0 ^a	46.0 ± 10.8	41.3 ± 10.7 ^a	45.9 ± 11.5
Average CAG repeat number	44.3 ± 3.4 ^a	43.5 ± 3.1 ^a	44.5 ± 3.6 ^a	44.0 ± 3.3
Average duration of motor illness at assessment, y	6.4 ± 4.3 ^a	7.3 ± 5.3 ^a	7.2 ± 5.8 ^a	8.3 ± 5.4

Values are mean ± SD.

^aSignificant difference compared to control group (*p* < 0.05).

Table 2 Sex differences

	Women	Men	Interpretation
No. (%)	919 (49.7)	930 (50.3)	NA
Average age at assessment, y, mean $\pm$ SD	52.2 $\pm$ 12.0	51.4 $\pm$ 11.4	$t(1, 1,847) = 1.54, p = 0.124$
Unadjusted average age at motor onset, y, mean $\pm$ SD	44.8 $\pm$ 11.2	44.0 $\pm$ 10.8	$t(1, 1,847) = 1.57, p = 0.117$
Age at motor onset, y (controlling for CAG), mean $\pm$ SE	44.8 $\pm$ 0.25	44.0 $\pm$ 0.25	$F_{1, 1,849} = 4.7, p = 0.030$
Average duration of motor illness at assessment, y, mean $\pm$ SD	7.4 $\pm$ 5.3	7.3 $\pm$ 5.1	$t(1, 1,847) = 0.14, p = 0.886$
Average CAG repeat number, mean $\pm$ SD	44.1 $\pm$ 3.4	44.1 $\pm$ 3.3	$t(1, 1,847) = -0.11, p = 0.909$
Current tobacco abuse, n (%) ^a	306 (42.7)	260 (48.0)	$\chi^2(1, 1,258) = 3.41, p = 0.065$
Lifetime alcohol abuse, n (%) ^a	127 (23.6)	247 (46.7)	$\chi^2(1, 1,066) = 62.122, p < 0.0001$
Lifetime drug abuse, n (%) ^a	76 (15.6)	141 (33.3)	$\chi^2(1, 909) = 38.967, p < 0.0001$

^a Compared to frequencies among patients who never abused substances.

According to the 2015–2020 dietary guidelines for Americans, moderate alcohol abuse is considered 1 alcoholic unit per day for women and 2 alcoholic units for men.⁸ Therefore, for the current study, participants reporting consumption of ≥ 14 units per week (regardless of sex) were classified as current alcohol abusers. The lifetime alcohol abuse category comprised patients who reported a positive history of alcohol problems and those patients determined to be heavy alcohol users (figure 2B).

Combining these 2 groups together, the average AMO of individuals using alcohol after controlling for CAG repeat length and sex was 1.0 years earlier compared to the control group. While these results were significant based on the p value (0.04), the calculated effect size was low (0.13), suggesting a small effect.

Women who abused alcohol had an average AMO that was 1.3 years earlier than women who did not abuse alcohol. Male alcohol abusers, on the other hand, had an AMO that was 0.9 years earlier than men in the control group (table 3).

Drug abuse decreases the AMO of HD. Drug abuse is thought to cause rapid and dramatic neurotoxicity, even after only minimal abuse. As a result, participants who reported past drug abuse were combined with participants who reported that they were currently abusing drugs to create the lifetime drug abuse group (figure 2C). Again, the questions asked of participants in the Enroll-HD database make it difficult to determine the temporal relationship between drug abuse and AMO. By including all patients who have a reported drug abuse history, it is unlikely that a significant number of patients were included who began abusing drugs after their AMO.

The average AMO of the lifetime drug abuse group after controlling for CAG repeat length was 3.3 years earlier than the control group (table 3).

The calculated effect size was 0.43. Drug abuse seems to have a substantial effect on the AMO of patients with HD.

The average AMO of women who abused drugs was 4.6 years earlier than women in the control group (effect size 0.61) and the average AMO of men who abused drugs was 2.5 years earlier than men in the control group (effect size 0.34). Of the 217 total participants in the drug abuse group, 85 (39.2%) participants reported only marijuana use. Over half of the participants (113) had a history of abusing at least one of the following drugs: amphetamines, methylphenidate, heroin, cocaine, club drugs (ecstasy), or hallucinogens. Eighty-four participants (38.7%) had a history of abusing at least 2 of the substances outlined in Methods. Only 5 (2.3%) participants were exclusively abusing barbiturates, tranquilizers, or painkillers.

Sex effect of substances on AMO. A sex interaction effect analysis was conducted to determine if the differences in AMO between men and women within the abuse categories was statistically significant. In the tobacco abuse group, this analysis yielded a p value of 0.461 ($F_{1, 1,258} = 0.544$) and 0.665 ($F_{1, 1,066} = 0.187$) in the alcohol abuse group. Interestingly, in the drug abuse group, the p value was 0.069 ($F_{1, 909} = 3.324$).

DISCUSSION Participants who abused substances had a significantly earlier AMO compared to the control group. These results were most striking in the drug abuse group. The findings provide a potential opportunity for practitioners to intervene in a risk-free way that may significantly delay the onset of motor symptoms, independent of pharmaceutical interventions, in patients with HD who abuse substances. The current lack of disease-modifying therapies for patients with HD exemplifies the clinical significance of this study.

Figure 2 Substance abuse groups

A. Tobacco abuse group

B. Lifetime alcohol abuse group

C. Lifetime drug abuse group

It is important to emphasize the size of this effect. For example, women abstaining from the use of drugs delayed the AMO by 4.6 years. Such an effect seen in the setting of a drug trial would be considered an important and clinically significant effect. Even in the most commonly used substance, tobacco, abstinence from smoking provided a protective effect of 2.3 years, on average.

The average, adjusted AMO for women in all of the substance abuse groups was lower than that of

men. However, the interaction statistic was not significant for any category. As the effects for both men and women were in the same direction (substances decreasing AMO), the threshold to cross significance for an interaction term is high and may obscure clinical significance. For instance, the effect of lowering AMO in women who abuse drugs is 2.1 years greater than in men, yet the interaction analysis was nonsignificant ($F_{1, 909} = 3.324, p = 0.069$). However, a difference of 2.1 years is nearly as much as the 2.3 years seen in the combined sample for tobacco use, which was highly significant ($F_{1, 1,258} = 33.8, p < 0.0001$). The findings support a previous study that reported that the effects of substances (alcohol and drug abuse) seemed to have a more dramatic effect on women than men.⁵ However, a few reports have demonstrated that women in general may be more susceptible to the adverse effects of substances of abuse,^{9–11} suggesting the effect is not specific to HD.

The exact mechanism by which these substances affect the AMO is unknown; however, the results of this study provide information that should be used to expand our knowledge on the pathophysiology of HD. In mouse models, the concentration of dopamine after the administration of various substances was measured in the accumbens and caudate. Amphetamine and cocaine were associated with the highest concentrations, followed by cocaine, then nicotine, and finally alcohol.¹² By extrapolating this information to the results of the current study, which showed that drug abuse is associated with the earliest AMO, followed by tobacco and alcohol abuse, increased dopaminergic activity may be associated with an earlier AMO. Further studies are needed to more definitively link monoamines and AMO in patients with HD.

Strengths of this study include the large number of participants from all across the world, as well as our ability to control for CAG repeat length. Past studies examining the effects of certain substances did not adjust for CAG length even though this is known to be the most important determining factor in the AMO.

There are several limitations of this study. Perhaps most important is the difficulty in determining a temporal relationship between substance abuse and the AMO. Every effort was made to ensure that only participants who were most likely to be abusing substances prior to their AMO were included, but it is impossible to determine this with absolute certainty. To that point, it is possible that participants with premanifest HD are more likely to abuse substances when motor symptoms are initially perceived. It is not known if this pattern of substance abuse actually occurs in patients with HD; however, such a phenomenon would make it more difficult to associate causality between

Table 3 Results

	Age at onset (adjusted for CAG repeat number), mean ± SE	Difference in average AMO between users and nonusers, y	F	p Values
All participants				
Tobacco abuse ^a				
Current tobacco abuse	43.2 ± 0.30	2.3	F _{1, 1,258} = 33.8	<0.0001
Never abused substances	45.5 ± 0.27			
Alcohol abuse ^a				
Lifetime alcohol abuse	45.3 ± 0.40	1.0	F _{1, 1,066} = 4.2	0.04 ^b
Never abused substances	46.3 ± 0.29			
Drug abuse ^a				
Lifetime drug abuse	42.3 ± 0.52	3.3	F _{1, 909} = 29.7	<0.0001
Never abused substances	45.6 ± 0.29			
Women only				
Tobacco abuse ^c				
Current tobacco abuse	43.5 ± 0.42	2.7	F _{1, 716} = 22.9	<0.0001
Never abused substances	46.2 ± 0.36			
Alcohol abuse ^c				
Lifetime alcohol abuse	45.3 ± 0.68	1.3	F _{1, 537} = 2.6	0.105
Never abused substances	46.6 ± 0.38			
Drug abuse ^c				
Current drug abuse	41.8 ± 0.89	4.6	F _{1, 486} = 22.5	<0.0001
Never abused substances	46.4 ± 0.38			
Men only				
Tobacco abuse ^c				
Current tobacco abuse	42.7 ± 0.42	2.0	F _{1, 542} = 11.2	0.001
Never abused substances	44.7 ± 0.44			
Alcohol abuse ^c				
Lifetime alcohol abuse	45.1 ± 0.47	0.9	F _{1, 529} = 1.7	0.187
Never abused substances	46.0 ± 0.44			
Drug abuse ^c				
Current drug abuse	42.1 ± 0.62	2.5	F _{1, 423} = 10.4	0.001
Never abused substances	44.6 ± 0.44			

Abbreviation: AMO = age at motor onset.

^aAdjusted for sex and CAG repeat length.

^bDespite the *p* value < 0.05, the Cohen effect size was 0.13, indicating a nonsignificant difference between means.

^cAdjusted for CAG repeat length.

substance abuse and AMO. Recent studies have demonstrated that downstream single nucleotide polymorphisms (SNPs) that are independent of the CAG repeat in *HTT* may affect the AMO in patients with HD.¹³ Limitations of the Enroll-HD database prevented us from controlling for such SNPs. The retrospective nature of this analysis is another limitation, as well as the fact that classification of patients into abuse categories was based on participant and family reports. A longitudinal, prospective study would need to be conducted to more definitively estimate the true effect of exposure to substances on AMO. Finally, it is

possible that there is crossover between groups. For example, it is possible that of the 566 participants in the tobacco abuse group, some of them may have abused alcohol or drugs at some point.

The clinical implications of these findings are substantial. There are currently no disease-modifying therapies available for patients with HD, and historically there have not been any patient-dependent factors that could modify the course of HD. However, these findings may provide a simple and risk-free intervention to recommend to premotor manifest patients that could add years without motor symptoms

to their lives independent of pharmaceutical interventions. Identifying other environmental factors associated with the AMO is necessary to continue to provide the highest level of care to patients with HD.

AUTHOR CONTRIBUTIONS

Jordan L. Schultz: study concept and design, acquisition of data, statistical analysis, development and editing of manuscript. John A. Kamholz: study concept and design, analysis and interpretation of data, development of manuscript. David J. Moser: study concept and design, analysis and interpretation of data. Shawna M.E. Feely: interpretation of data, manuscript development. Jane S. Paulsen: Enroll site principal investigator, acquisition of data, analysis and interpretation of data, development and editing of manuscript. Peg C. Nopoulos: study concept and design, analysis and interpretation of data, development and editing of manuscript.

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DISCLOSURE

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