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Research Report

Antidopaminergic Medication is Associated with More Rapidly Progressive Huntington's Disease

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Abstract.
Background: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder leading to progressive motor, cognitive and functional decline. Antidopaminergic medications (ADMs) are frequently used to treat chorea and behavioural disturbances in HD.
Objective: We aimed to assess how the use of such medications was associated with the severity and progression of the motor aspects of the condition, given that there have been concerns that such drugs may actually promote neurological deterioration.
Methods: Using multiple linear regression, supplemented by principal component analysis to explore the overall correlation patterns and help identify relevant covariates, we assessed severity and progression of motor symptoms and functional decline in 651 manifest patients from the REGISTRY cohort followed for two years. ADM treated versus non-treated subjects were compared with respect to motor impairment at baseline and progression rate by means of multiple regression, adjusting for CAG-repeat and age.
Results: Patients treated with ADMs had significantly worse motor scores with greater functional disability at their first visit. They also showed a higher annual rate of progression of motor signs and disability over the next two years. In particular the rate of progression for oculomotor symptoms and bradykinesia was markedly increased whereas the rate of progression of chorea and dystonia was similar for ADM and drug naïve patients. These differences in clinical severity and progression could not be explained by differences in disease burden, duration of disease or other possible prognostic factors.
Conclusions: The results from this analysis suggest ADM treatment is associated with more advanced and rapidly progressing HD although whether these drugs are causative in driving this progression requires further, prospective studies.

Keywords: Huntington disease, observational study, dopamine, antipsychotics, tetrabenazine

INTRODUCTION

Huntington's disease (HD) is a dominantly inherited neurodegenerative disease characterized by abnormalities of movement control, cognitive decline, and psychiatric illness as well as weight loss. The motor

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disorder typically is mixed with differing degrees of parkinsonism, dystonia, ataxia and chorea. Although chorea remains the most representative clinical manifestation of HD, it's impact on the patients' disability seem to be less important than the progressively impaired voluntary motor dysfunction and some of their cognitive and psychiatric problems [1, 2]. Phenoconversion (i.e. the change from premanifest to manifest disease) occurs usually in mid-life, followed by a relentless progression with functional decline leading to premature death in the majority of cases. Considerable advances in the understanding of the underlying pathophysiological mechanisms have been made since the gene for HD was discovered in 1993, but the medical treatment of HD has made relatively little progress over this time and no treatment recommendations could be made in a recent evaluation of 20 randomized controlled clinical trials in HD patients [3].

Despite insufficient clinical evidence for long term safety and efficacy in the treatment of HD, dopamine depleting and dopamine blocking antipsychotic medications (ADMs) are frequently prescribed to treat chorea and/or behavioural symptoms as well as the weight loss in some cases. In a recently published Europe-wide assessment of current medication choices in HD, 84% of patients received symptomatic medication such as antipsychotics and antidepressants [4].

Several potentially persistent neurobiological adverse effects have been associated with the long term use of ADMs including the development of tardive dyskinesias, dystonia and parkinsonism [5]. Many genes and proteins modulated by antipsychotic drugs are involved in synaptic function and energy metabolism [6, 7] including pathways implicated in HD pathogenesis [8]. There is also emerging experimental evidence that their long term use can be associated with pathology. For example, studies in macaque monkeys suggest that prolonged haloperidol and olanzapine treatment can be associated with decreased brain weight especially in the frontal and parietal lobes, with decreased astrocyte numbers, dendritic arborisation and dendritic spine density [9, 10]. Indeed there is also some evidence that this can be seen in patients - for example long term neuroleptic treatment is associated with decreased brain volumes in schizophrenic patients [11, 12]. In addition to overall brain volume decrease, some studies have suggested increased basal ganglia volumes following antipsychotic treatment different following treatment with atypical vs atypical antipsychotics [13]. However, a recent review based on longitudinal monotherapy data suggests inconclusive results. Effects induced by treatment with typical antipsychotics could not be confirmed, while both volumetric increases and decreases in the basal ganglia were observed after treatment with atypical antipsychotics [14]. It should also be noted that antipsychotic treatment is reported to be associated with worsening of dementia in Alzheimer's disease, suggesting that such medications may be harmful in vulnerable populations, such as in neurodegenerative disorders [15]. In HD it has been observed in several studies that patients that are treated with antipsychotivc medications display a more severe clinical phenotype [16–18].

In this study we now sought to investigate the relationship between the use of ADM treatment and HD severity and rate of progression using a large retrospective analysis of data collected as part of the EHDN registry study.

METHODS

We used monitored data from the European Huntington Disease Network (EHDN) Registry study which was established in 2004 to collect phenotypical data and biomaterials from a large group of patients with HD. More information about the Registry cohort can be found at http://www.euro-hd.net/html/registry.

We received data on 889 patients, with a first visit occurring between 1997 and 2008. Subjects underwent 1–9 visits with clinical assessments over a time of 26–469 weeks following inclusion in the study. To a large extent, visits were performed annually. Demographic data included age, gender, and age at onset was collected with the latter defined as the age at which the first motor, cognitive, or behavioural signs of HD appeared, according to the rater. CAG repeat sizes were available for all subjects. Disease burden scores, a measure of the integrated lifelong exposure to mutant huntingtin, were calculated according to the formula; age at visit 1* (CAG-35.5) [19]. Motor signs and functional status were assessed using the Unified Huntington Disease Rating Scale (UHDRS), and was recorded at all visits. Medication (name, indication, start and stop date) were available for a majority of subjects. To qualify as a patient treated with ADMs the patient should have been treated with an antipsychotic drug (typical and atypical neuroleptics including tiapride) or tetrabenazine for at least half of the follow up time. Full ethical approval has been obtained for each European country contributing to the Registry study. All subjects gave written informed consent.

STATISTICAL ANALYSIS

Descriptive statistics in terms of ADM treatment (YES/NO) was generated for demographic variables and UHDRS motor and functional measures. UHDRS motor items were summarized as Total Motor Score (TMS) (motor items 1–15), mMS (items 4–10, 13–15), dystonia (item 11), chorea (item 12), and eye movements (items 1–3). Functional measures included total functional capacity (TFC), Independence (IS) and functional checklist (FA). UHDRS between-group comparisons using student's *t*-test were made for all variables.

Principal component analysis (PCA) [20] was applied to the combined data on demographics, baseline UHDRS scores, and annualised progression rate, to obtain an overview of the correlations present in the material. Separate PCA models were also generated for each treatment group to check for consistency and potential confounding effects of ADM treatment. For PCA, zero mean and unit variance scaling was applied to all variables. Statistical significance was determined by cross-validation. Based on the correlations revealed by PCA, a multiple linear regression model was generated to analyse the impact of ADM treatment on global motor impairment at baseline, measured as TMS at the first visit. This model included ADM treatment as an independent factor, and age, disease burden and duration of disease as covariates. Other factors considered were CAG size, and gender. The explanatory factors included in the final model were selected considering the statistical significance of each factor, collinearity among the independent variables, and model validity judged by analysis of residuals, in order to obtain an optimal regression model. To assess the effects of ADMs on hypokinetic versus choreatic motor signs, similar regression models were also made using the mMS and chorea subscales as dependent variables. Furthermore, the effect of ADM treatment on progression rate was analysed by means of a multiple linear regression model with annualised TMS progression rates as the dependent variable, ADM treatment as an independent factor, and CAG repeat count, and baseline severity (first visit TMS) as additional independent variables. For the regression models, statistics and regression parameters are shown, along with confidence intervals derived using model based and robust covariance estimators. In addition, for the main variables of interest, i.e., TMA and FA, and their progression rates, statistics are also shown for the "unadjusted" effect of antidopaminergic treatment, i.e., derived from models with antidopaminergic treatment as the only independent variable, for comparison. PCA calculations were performed using Simca P 12.0 (Umetrics, Inc.). Multiple regression was performed using IBM SPSS version 20.

RESULTS

Demographics of study population: Following the medication review, 651 patients (73%) had records of sufficient detail to be included in the analysis. In this group 320 patients were treated with ADMs and 331 without such medication. For patients treated with ADMs the mean duration of treatment was 2.7 (SD 4.5) years before visit 1 in this observational study. The main reasons given for starting ADM treatment were chorea (70%), followed by behavioural disturbances (18%). The five most commonly used ADMs were olanzapine, tiapride, haloperidol, tetrabenazine and risperidone. The average follow up time was 2.0 (SD 1.1) years for patients without ADM treatment and 2.0 (SD 1.3) years for patients with ADM treatments. Detailed baseline demographic data is given in Table 1. In addition to ADMs, a wide variety of medications were recorded. Antidepressants were prescribed to 43% of the ADM naïve and 62% of the ADM treated subjects. Memantine, hypothesised to possess neuroprotective properties [21], were prescribed to 12 ADM naïve group and 14 ADM treated subjects. Valproate, also putatively neuroprotective [22], was prescribed to 10 naïve and 30 ADM treated subjects.

Assessment of the overall correlational structure using PCA, generated similar models for each of the two treatment cohorts, as for the combined data set.

Table 1
Baseline characteristics for patients with and without concomitant Anti Dopaminergic Medication (ADM) treatment

	Untreated	ADM treatment
N	331	320
Follow up time (yrs)	2.0 (1)	2.0 (1.2)
Age	49 (13)	53 (12)***
CAG	44.5 (5)	44.3 (4)
Disease burden score	401 (123)	429 (115)**
TMS (Total motor score, items 1-15)	26.6 (19)	41.7 (21)***
mMS (modified motor score, items 4–10, 13–15)	11.7 (9)	18.5 (10)***
Oculomotor score (items 1–3)	6.2 (6)	9.3 (6)***
Chorea (Item 11)	6.9 (5)	10.4 (6)***
Dystonia (Item 12)	1.8 (3)	3.5 (4)***
TFC (total functional capacity)	9.7 (3)	7.1 (4)***
FA (functional assessment)	20.7 (5)	16.4 (7)***
IS (independence scale)	86.1 (15)	73.7 (17)***

Values represent mean (SD). ***$p < 0.001$; **$p < 0.01$, *Untreated vs. ADM treated, by students *t*-test.

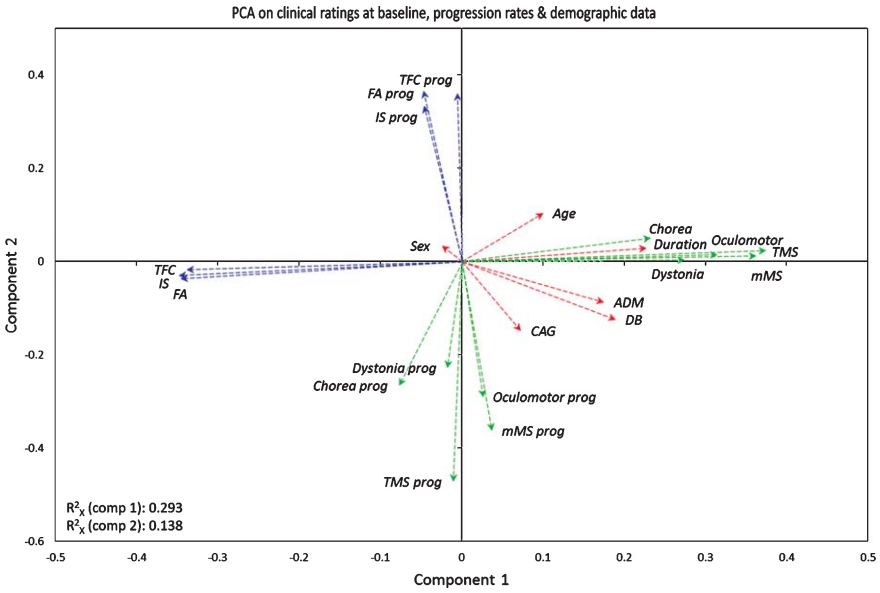

Fig. 1. Variable loadings from PCA on demographics, baseline clinical variables and progression rates. Variable loadings for component 1 (horizontal axis) are plotted vs. loadings on component 2 (vertical axis), loadings for each variable drawn as a vector to emphasize magnitudes and directions. This plot illustrates the overall pattern of correlations present in the dataset analysed. Variables located close to each other, i.e., with loadings of similar direction and magnitude, covary. Variables located in orthogonal directions from the origin are uncorrelated. Variables located close to the origin have little covariance with the other variables in the dataset. As an example, motor scores at baseline, higher scores indicating more severe symptoms, are inversely correlated to functional measures, higher scores indicating better function (opposing positions along component 1). Similarly, the rate of progression of motor symptoms is inversely correlated to the rate of progression on functional measures (component 2). Baseline clinical scores were: UHDRS total motor score (TMS), and subscales: mMS, chorea, dystonia, oculomotor, and functional assessment (fa), total functional capacity (tfc), and independence scale (is). "Prog" denotes annualised progression rates on these scales. ADM: antidopaminergic medication, DB: Disease burden.

In brief, a significant, four component PCA model describing 62% of the variance, with a Q^2_{cum} at 36% was obtained for the full data set. The first component ($R^2X = 29\%$, $Q^2 = 25\%$) showed a very high degree of covariance between all UHDRS motor measures, which were negatively correlated to the functional measures (TFC, IS and FA). Among the different motor subscales, although these covaried, chorea had a notably smaller loading (position along component 1) compared to the mMS subscale, suggesting that mMS was more strongly negatively correlated to the functional scores. It was also evident that ADM treatment, higher disease burden scores, age, and longer duration of disease, were all associated with worse scores with respect to functional and motor severity. The second PCA component ($R^2X = 14\%$, $Q^2 = 7\%$) represents the measures of disease progression, which was to some extent associated with disease burden and CAG repeat length. A variable loading plot, illustrating these results (first two components) is shown in Fig. 1. Similar results on PCA performed on these data have been presented previously [23]. The third and fourth components ($R^2X = 10\%$, $Q^2 = -0.03$, $R^2X = 9\%$, $Q^2 = 0.1$, respectively) represented mainly the inverse relationship between CAG repeat length and age found in all cross-sectional samples of patients with HD. Furthermore, the fourth component suggested a negative correlation between baseline severity and progression rate, interpreted as a ceiling effect. Based on the strong positive correlation between TMS and all other motor scores, and the equally strong negative correlation between motor and functional scores, TMS was chosen for subsequent analyses. The PCA results also guided the choice of relevant covariates for the multiple regression models.

Clinical severity

Patients treated with ADM had significantly higher motor scores and lower TFC scores as compared to patients without such medication, as analysed by *t*-tests. Interestingly, patients treated with ADMs also had higher scores for the chorea item of the UHDRS motor assessment. Baseline clinical data is given in more detail in Table 2. Patients treated with ADMs were on average 2.7 years older, had a somewhat longer estimated duration of HD (2.8 years) and accordingly a larger disease burden, but had similar CAG repeat

Table 2
Annualized progression (units) for motor and functional scores of UHDRS motor and functional assessment

	Untreated	ADM treatment
TMS (Total motor score, items 1–15)	3.7 (7)	4.8 (8)
mMS (modified motor score, items 4–10, 13–15)	1.8 (4)	2.7 (4)**
Oculomotor (items 1–3)	0.9 (3)	1.6 (3)**
Chorea (item 11)	0.6 (3)	0.1 (4)
Dystonia (item 12)	0.4 (2)	0.4 (2)
TFC (total functional capacity)	−0.7 (2)	−1.1 (2)**
FA (functional assessment)	−1.1 (2)	−2.0 (3)***
IS (Independence scale)	−3.7 (7)	−5.7 (7.7)***

Values are mean (SD). ***$p < 0.001$; **$p < 0.01$, *$p < 0.05$ Untreated vs. ADM treated, by students *t*-test. ADM: antidopaminergic medication.

lengths, as compared to the non-treated group. The correlation between baseline TMS and its major determinant, disease burden, is shown by treatment group in Fig. 2, showing a clear off-set towards higher TMS scores at a given disease burden score in the ADM treated group. Furthermore, the multiple regression model of disease severity measured as TMS score indicated a significant effect of ADM treatment ($p < 0.001$, Table 3), when controlling for disease burden, age and duration, which were significant independent variables ($p < 0.001$, $p = 0.002$, $p < 0.001$). Hence, differences in baseline clinical severity could not be fully explained by clinical/demographic factors available in this data set. The auxiliary multiple regression models on the chorea and mMS subscales indicated a significant effect of ADM on mMS, reflecting voluntary/hypokinetic motor signs, as well as on chorea (Table 3).

Progression of disease

The progression of motor and functional decline was faster in ADM treated patients across all domains analysed, except for the involuntary motor symptoms i.e. chorea and dystonia (Table 2). To assess whether this observation was related to differences in demographic or baseline characteristics, multiple regression modelling with TMS annualised progression rate as the dependent variable, and ADM treatment as an independent factor was performed. Additional independent variables considered were baseline TMS, disease burden, age, and CAG repeat count. This analysis indicated that the progression rate was significantly higher in the ADM treated patients, $p = 0.0023$, Table 4, when controlling for CAG and baseline TMS, which were both significant covariates ($p < 0.001$). The inclusion of disease burden and/or age as independent variables did not improve the model or affect the outcome appreciably. As an additional check, similar analyses were performed using baseline chorea as a covariate. Since chorea was the predominant reason for initiating ADM treatment this sign might represent some trait difference explaining the findings. However,

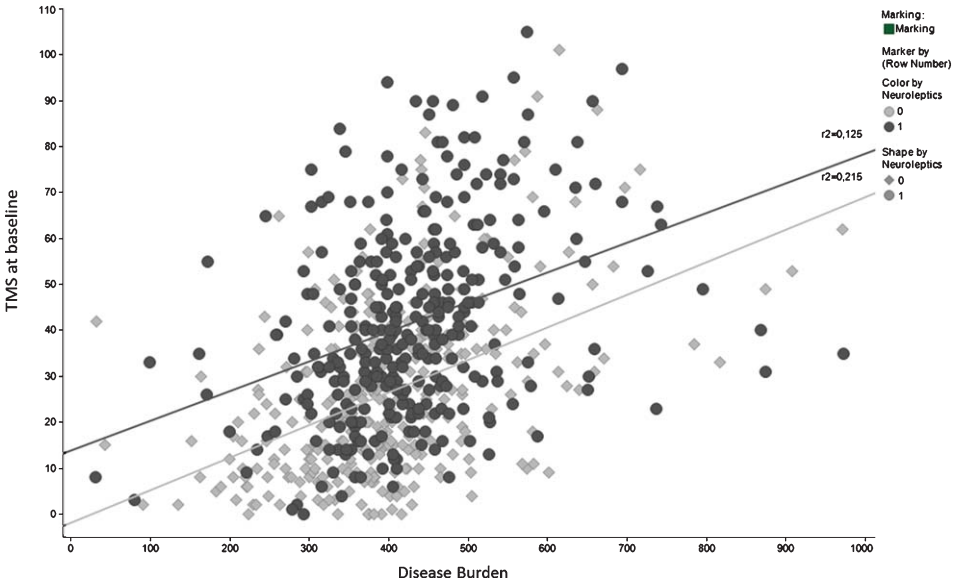

Fig. 2. Baseline severity (UHDRS total motor score, TMS, at first visit) vs. disease burden (DB), by antidopaminergic medication (ADM) (light grey: no ADM, dark grey: on ADM). Pearson's r squared is indicated for each subgroup, i.e., with or without ADM treatment ($p < 0.001$, both subgroups).

Table 3
Results from multiple linear regression models of TMS, chorea, and mMS (baseline value)

Dependent variable	Factor	Slope	CI	p	Slope Std	CI robust
TMS R2 = 0.395, R2adj = 0.391 $p < 0.001$	ADM	9.1	6.4–11.8	<0.001	0.21	6.4–11.8
	DB	0.0625	0.052–0.073	<0.001	0.35	0.049–0.076
	Age	0.17	0.065–0.28	0.002	0.10	0.065–0.028
	Duration	1.27	1.0–1.53	<0.001	0.33	0.96–1.6
TMS, unadjusted model R2 = 0.125 R2adj = 0.123 $p < 0.001$	ADM	15.0	12.0–18.1	<0.001	0.35	
Chorea R2 = 0.20 R2adj = 0.196	ADM	2.4	1.6–3.3	<0.001	0.22	1.6–3.2
	DB	0.008	0.05–0.011	<0.001	0.17	0.004–0.012
	Age	0.080	0.047–0.11	<0.001	0.18	0.047–0.11
	Duration	0.18	0.10–0.26	<0.001	0.18	0.077–0.29
mMS R2 = 0.373 R2adj 0.369	ADM	4	2.7–5.3	<0.001	0.19	2.6–5.3
	DB	0.03	0.025–0.036	<0.001	0.35	0.024–0.036
	Age	0.075	0.023–0.128	0.005	0.093	0.023–0.127
	Duration	0.61	0.49–0.74	<0.001	0.32	0.47–0.76

Shown are regression coefficients for each independent variable, with p-values and 95% confidence intervals (CI). Slope std: standardized regression coefficients. CI robust: CI derived from robust covariance estimation, ADM: antidopaminergic medication.

Table 4
Results from multiple linear regression model of TMS (UHDRS total motor score) progression rate

Dependent variable	Factor	Slope	CI	p	Slope Std	CI robust
TMS Progression rate R2 = 0.034, R2adj 0.029 $p < 0.001$	ADM	2.0	0.76–3.26	0.002	0.13	0.802–3.22
	Baseline TMS	−0.06	−0.089 – −0.030	<0.001	−0.17	−0.088 – −0.031
	CAG	0.188	0.050–0.326	0.008	0.11	0.038–0.338
TMS Progression rate, unadjusted model R2 = 0.005, R2adj 0.004	ADM	1.1		0.07	0.07	

Shown are regression coefficients for each independent variable, with p-values and 95% confidence intervals (CI). Slope std: standardized regression coefficients. CI robust: CI derived from robust covariance estimation, ADM: antidopaminergic medication.

these models indicated that baseline chorea may have a negative correlation to TMS progression, both in the ADM naive and the ADM treated cohort, i.e. higher initial chorea scores appeared to be associated with somewhat slower progression (not shown). Thus severity of chorea would not explain the faster progression in ADM treated patients.

Auxiliary analyses

The main analyses performed indicated a clear difference between ADM- naïve and ADM treated subjects in terms of both clinical severity and progression. To further explore this finding, additional exploratory analyses were performed using factors representing different subtypes of antidopaminergic medications; tetrabenazine, typical antipsychotics, and atypical antipsychotics. Since such medications were often used in combination, the different classes could not be analysed in separate subgroups. Covariates were the same as for the main models described above. The models obtained showed similar effects independent on type of ADM, suggesting no major differences in this respect: For TMS the following was obtained: Tetrabenazine, 3.8 ($p = 0.055$), typical antipsychotics 6.1 ($p = 0.001$), atypical antipsychotics 6.3 ($p < 0.001$) points vs. naïve; TMS progression rate (pts/year): Tetrabenazine 2.0 ($p = 0.029$), typical antipsychotics 1.8 ($p = 0.024$), atypical antipsychotics 1.5 ($p = 0.025$) vs. naïve.

Furthermore, the potential influence of country was explored. The distribution of ADM naïve and ADM treated subjects in the 6 major contributing countries covering >90% of the subjects in the final data set was as follows: Overall percentage of ADM treated subjects: 49%, UK 34%, Germany 53%, Italy 70%, Netherlands 39%, Poland 67% Spain 53%. To check whether the differences between treated vs naïve subjects observed were driven by differences between countries, separate analyses for each of the major contributing countries (UK, Italy, Germany, Holland) as well as an analysis excluding these countries, were performed, all yielding similar results. For example, analysing German subjects only, ADM treated had 8.0 points higher TMS scores ($p < 0.02$) and 2.8 points faster yearly TMS progression rate ($p = 0.094$) compared to naïve subjects. Thus, differences related to country cannot explain the effects of ADM treatment suggested by the present analyses. Finally, the potential impact of indication for initial prescription of ADM

was investigated by creating regression models of TMS and TMS progression based on ADM treated subjects categorised by indication: motor, behavioural symptoms, or both. These models used indication categories as independent factors, and the same covariates as in the main models described above. ADM indication was available for 287 subjects in the final data set: 167 (motor), 95 (behaviour), and 15 (both). No differences related to indication in either TMS or TMS progression were suggested (i.e., no significant effect or trends towards effects of indication on these outcomes were observed).

DISCUSSION

We found that ADM treated patients displayed a more severe clinical phenotype and a faster progression of voluntary motor dysfunction as well as functional decline. The analysis is based on retrospective data, which carries the risk of uncontrolled factors and potential selection bias influencing the outcome. Thus, while these findings suggest that the use of ADMs in HD could contribute to a more rapid motor progression based on clinical assessments, this will need to be studied prospectively before any firm conclusions can be drawn. Medications that counteract dopaminergic functions have well known side effects, including parkinsonism, and since a substantial part of the HD motor phenotype is associated with such negative motor features, it is likely that ADM treatments could further enhance such signs. Hypokinesia is closely linked to independence in HD [24], and in this study patients treated with ADMs also showed a higher degree of functional impairment although it is not possible to say that these are causally linked.

In this cohort, baseline motor function (TMS) was significantly worse in ADM treated patients, including more severe oculomotor and voluntary motor dysfunction, as well as a higher degree of chorea and dystonia. This finding is in agreement with what has been previously observed in observational studies [25], as well as in randomized clinical trials [26]. We also observed a significant impact of ADM treatment on the progression rate of motor impairment. Considering motor subscales, ADM treated patients showed substantially increased progression of their voluntary motor disorder, whereas the progression of the involuntary motor disorder was less as compared to treatment naive patients. Accompanying these effects was also a higher rate of functional decline in ADM treated patients.

One explanation to our findings is that ADMs are preferentially prescribed to patients with a more aggressive type of HD, although multiple regression models controlling for CAG and baseline score did seem to confirm an independent effect of ADM medication on the progression rate.

The long term efficacy and safety of ADM treatment is inadequately studied in HD patients. A number of clinical trials involving neuroleptic treatment in HD have been published and such reports could possibly be a reason for the widespread off label use of such medications as well as personal observations made by experienced clinicians. However, recent research aiming for an evidence based guideline for the use of neuroleptics in chorea management concluded that data are insufficient to make recommendations regarding ADM use in HD [27]. A study recently published on a French cohort compared different ADMs with respect to motor, behavioural and functional decline in HD over 8 years [28]. This cohort displayed similar baseline characteristics and progression rates as reported herein, and concluded that the ADMs analysed appeared similar with respect to motor decline, while some differences were observed regarding functional decline which seemed less severe in subjects treated with dibenzodiazepines. No conclusions could be provided as to the efficacy of ADMs as such versus no ADM treatment in HD, however it was noted that non-treated subjects were less severely affected.

In conclusion, this analysis of European Registry data shows that the use of ADMs in HD is associated with patients with a worse prognosis. Whether this is due to the drugs themselves or to some type of selection bias or other unknown factors cannot, given the caveats with retrospective data analysis, be resolved, but does merit further investigation with prospective, randomized long term clinical trials.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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