Exploring the association between antidepressants, progression and mortality in Huntington's disease

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Abstract

Psychiatric symptoms are very common in Huntington's disease (HD). In keeping with other neurodegenerative diseases, there are concerns that antidepressants may worsen disease progression. Previous work on antidepressant effects in HD has been limited by confounding by indication, small sample sizes, short follow-up or a combination of these. We leveraged data from the ENROLL-HD (25550 participants) cohort to determine if 1) symptoms associated with antidepressant initiation are associated with faster disease progression and 2) antidepressants have an impact on disease progression and mortality in people with HD (pwHD) experiencing these symptoms.

We first determined the commonest indications for antidepressant prescription in pwHD. We selected adult pwHD (age ≥18, genetically confirmed HD), not on antidepressants and free of antidepressant-indication symptoms at baseline, (N=6166) and used linear mixed models to determine the association between symptoms listed as indications for antidepressant prescription and disease progression and mortality. Using propensity score weighting, we selected adult pwHD who remained antidepressant-naive until an episode of antidepressant-indication symptoms (N=1877) and compared disease progression and mortality between those starting an antidepressant (N=194) before the next follow-up versus those who did not (N=1683). Outcomes were 1) disease progression measured by the composite disease score in ENROLL-HD; and 2) mortality.

Depression and anxiety accounted for >80% of indications for antidepressant prescription in pwHD: episodes of depression/anxiety (experienced by 3131/6166) were associated with increased composite disease score progression from 0.46 to 0.52/year ($p=3.1x10^{-11}$), and increased mortality (Hazard Ratio=1.5,$p=9.4x10^{-6}$). In pwHD with new depression/anxiety free of antidepressants at symptom onset, antidepressant initiation (N=194/1877) 1) reduced composite disease score decline from 0.89 to 0.53/year (p=0.002); and 2) reduced all cause mortality(Hazard Ratio 0.38,p=0.04). An exploratory analysis of antidepressant

classes showed that TCAs reduced suicide and non-suicide mortality; SSRIs and atypical agents reduced suicide risk, whilst SNRIs reduced non-suicide related mortality.

Depression and anxiety are associated with more rapid disease progression and increased mortality in HD. In pwHD affected by depression and anxiety, antidepressant initiation slows disease progression and reduces mortality risk, with preliminary evidence of antidepressant-class specific reduction in both suicide and non-suicide mortality risk. This finding warrants further investigation in both HD and other neurodegenerative diseases.

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Introduction

Psychiatric symptoms are very common in Huntington's disease (HD); a progressive neurodegenerative disorder focussed on cortico-striatal networks, that is caused by a CAG repeat expansion in the *Huntingtin* gene[1]. The commonest psychiatric symptoms in HD are depression, irritability and apathy[2]. These symptoms have a significantly higher impact on function and quality of life in HD than motor impairments do[3]. Consequently, antidepressants and other psychoactive medications are very frequently prescribed to patients with HD[4].

The evidence base supporting the use of psychoactive medication in HD is limited: no randomised controlled trials of antidepressants for depression as a primary outcome in HD have been performed, or are listed on trial registries. Furthermore, evidence from other neurodegenerative diseases such as Alzheimer's disease suggest that antidepressants are ineffective for depression[5]; and psychoactive medication is associated with higher all-cause mortality in people with dementia[6]. In HD specifically, recent work has suggested faster disease progression in patients with HD treated with antidepressants[7].

However, observational studies showing excess mortality and/or faster disease progression in neurodegenerative diseases have not addressed confounding by indication. Prescription of antidepressants and other psychoactive medications may reflect more severe clinical symptoms (and potentially more severe neurodegeneration) necessitating more aggressive symptomatic treatment. Further to this, previous studies showing worsening clinical measures of disease progression in HD, have not determined the possible effect on mortality.

This work addresses the potential effects of antidepressants on disease progression by using data drawn from the largest observational study of HD: ENROLL-HD[8]. ENROLL-HD is a large international observational study of HD in which participants at all disease stages are followed longitudinally using a range of clinical assessments and self-report scales.

In this work, first we aimed to determine the frequency of common symptomatic indications for antidepressant initiation. Secondly we tested for an association between new episodes of these symptoms with both disease progression and mortality to test for confounding by

indication. Finally, in antidepressant-naive participants with new episodes of symptoms associated with antidepressant initiation, we compared both disease progression and mortality between those starting an antidepressant versus those who did not.

Materials and methods

For this study we used data from the ENROLL-HD observational study[8]. ENROLL-HD is an ongoing, worldwide observational study of people with HD and familial controls. Information is collected yearly with formal assessments of cognitive, psychiatric and motor symptoms, in addition to information on co-morbidities, medication, substance misuse and mental health (suicide attempts, admission to inpatient mental health facility admission). The most recent release (periodic data set 6 – PDS6) included data from 25 550 individuals, with the earliest data being collected in 2012(mean visit 3.06, visit range 1-15; including unscheduled visits). Death and suicide are captured as significant events in ENROLL-HD. ENROLL-HD adhered to the declarations of Helsinki, and all recruited patients were formally consented. Both studies received institutional approval from UK research ethics committees.

We included all patients aged 18 or over, with a confirmed genetic diagnosis of HD. We excluded any HD participants already receiving antidepressants at baseline study visit to compare the trajectories of disease progression after starting an antidepressant versus not starting one. We determined antidepressant use in the dataset as WHO ATC code N06A.

Psychiatric symptoms are measured by the Problem Behaviours Assessment(short form[8] - PBAs) Hospital Anxiety and Depression Scale(HADS[8]) in ENROLL-HD. The PBAs has multiple subscales measuring depressed mood, anxiety and 9 other psychiatric symptoms common in HD. Each symptom is scored from 0-4 on both severity and frequency, the product of severity and frequency ranges from 0-16. The HADS depression score (0-21) and anxiety score (0-21) are self-report scores, with higher scores indicating more severe symptoms. As the correlation coefficient between the scales is only moderate in pwHD in ENROLL-HD($0.43, p<2\times10^{-16}$), we determined an episode of psychiatric symptoms as the relevant PBAs subscale>4, or relevant HADS

subscale >7. Both scales have been validated in pwHD, including participants with cognitive impairment[9,10].

As clinical outcome variables in ENROLL-HD, we used the most reliable disease progression measure: composite disease score[11]. This comprises a combination of two cognitive task scores (Stroop word reading task – SWRT, and symbol digit modality task – SDMT[8]), the functional scale (total functional capacity – TFC) and the motor score from the unified HD rating scale[12] (UHDRS motor score). The composite disease score becomes more negative with increasing disease progression.

Mortality and suicide are captured in ENROLL-HD as specific events, and time in days from baseline study visit is recorded.

Statistical Approach

All analyses were conducted using R, an open source statistical analysis package, using the svy2lme, lme4, survey, Tipr, Sensemakr and Twang packages.

We first determined the commonest indications for antidepressant initiation, listing all indications from the following categories: depression, anxiety, irritability/aggression, psychosis, apathy, other psychiatric symptom, sleep, motor symptom of HD, pain, systemic illness, unclear (supplementary data Methods), and selected the most frequent indications for subsequent analyses.

To test for an association between indications for antidepressant initiation and clinical disease progression, we constructed a linear mixed model, with an outcome of the composite disease score, and included baseline composite disease score, baseline psychiatric scores, number of antidepressant prescriptions, comorbidity, addiction, psychoactive drug use, age, sex, and CAG repeat length (number of CAG repeats: NCAG) as co-variates. The independent variable was defined as episodes of indications for antidepressant initiation (modelled as a time-dependent

variable) in ENROLL-HD after baseline; we included subject as a random effect on intercept and slope. As exploratory analyses we tested for an association between individual symptoms scores modelled as time-dependent variables and clinical disease progression.

We used propensity scoring to determine the effect of antidepressants on disease progression. To avoid confounding by indication (antidepressants are most commonly prescribed to patients with more severe symptoms, who may have worse disease progression), we selected antidepressant-naive patients from ENROLL-HD with incident episodes of indications for antidepressant initiation, throughout the study and compared subsequent disease progression in those who started an antidepressant before the next follow-up, with participants who did not, in an intention to treat analysis. We included age; sex; total number of antidepressant changes; baseline scores for PBAs depression, PBAs suicidal ideation, PBAs anxiety, PBAs irritability; concurrent other psychoactive medication use (anti-dopaminergic medication, mood stabilisers, benzodiazapines); significant mental health event (suicide attempt or psychiatric hospital admission); multiple comorbidities(>5); and baseline composite disease score in the propensity scoring model. All variables were included in the outcome model in addition to the inverse propensity score in a doubly robust process as described in Funk et al[13]. We used linear mixed models to determine the relationship between antidepressant use and change in the composite disease score over time. We fitted Cox proportional hazard models to determine the effect of antidepressants on all cause mortality. As an exploratory analysis we fitted Cox proportional hazards for antidepressant effect on suicide and non-suicide death. As an additional sensitivity analysis, we determined the effect of antidepressant exposure (duration of antidepressant treatment) on any significant findings from the intention to treat analysis. As an exploratory analysis we determined the effect of individual antidepressant classes on disease progression and mortality. We used the nnet and simputation packages to compare missing data between treatment groups and impute missing data. Using the tipr and sensemakr packages in R, we conducted a tipping point analysis as described in McGowan[14]. To determine the effect of potential unobserved confounding on our findings, we calculated the partial R^2 (partial $R^2 = t^2/\{t^2+\text{degrees of freedom}\}$) of an unobserved confounding variable with both the outcome and exposure that would eliminate the association between antidepressant treatment over time and composite disease score . We then plotted this partial R^2 against exposure and outcome and compared this to the partial R^2 of known co-variates to

determine the likelihood of such a confounder existing. As an additional sensitivity analysis, we calculated the robustness value[14] (reported as percentage of residual variance in outcome explained by an unobserved confounder added to the model; Robustness Value = ½{f+4f-f}, where f equals the t-statistic of the exposure (antidepressant treatment over time) divided by degrees of freedom). The robustness value was compared to the percentages of outcome variance explained by the other co-variates in the model. Missing data did not differ between treatment groups (eMethods). We used a hierarchical approach to account for multiple comparisons: first testing for an association between psychiatric symptoms with disease progression and mortality to determine if confounding by indication was present; second testing the association of antidepressants on disease progression; and finally testing the association between antidepressants and mortality.

Results

Antidepressant Indication

The commonest indications for antidepressant use were anxiety and depression, accounting for over 80% listed indications (Table 1). We therefore selected incident episodes of depression or anxiety (psychiatric symptoms) after study entry as the indication for antidepressant initiation.

Association Between Psychiatric Symptoms and Disease Progression

In ENROLL-HD, 3131/6166 antidepressant-naive participants with HD who were free of psychiatric symptoms at baseline experienced an episode of depression or anxiety during the study(PRISMA-style[15] diagram explaining inclusion: Figure 1). The group with psychiatric symptoms were older, more likely to be female, with more advanced disease and larger NCAG (Table 2).

The linear mixed model examining the association between psychiatric symptoms (episode of anxiety or depression) and the composite disease score showed that having psychiatric symptoms was associated with faster progression. The composite disease score deteriorated by 0.46/year across all participants. A single episode of psychiatric symptoms was associated with faster deterioration of 0.06/year (95%CIs 0.042,0.078; $p=3.1x10^{-11}$)(Figure 2A, Supplementary Table 1). As an exploratory analysis, the individual symptom

score for depression was also significantly associated with more rapid progression of the composite disease score, but anxiety only approached significance (p=0.056)(Supplementary Table 2&3).

All cause mortality risk was associated with the presence of psychiatric symptoms (HR 1.5, $p=9.4x10^{-6}$)(Figure 2b, Supplementary Table 4). To determine if the association between increased mortality risk and psychiatric symptoms related to increased suicide rate, as an exploratory analysis mortality was separated into suicide and non-suicide mortality. These models showed that psychiatric symptoms were associated with increased non-suicide mortality but not with suicide risk (Supplementary Tables 5&6). Exploratory analyses of individual symptoms scores suggest that depression was more strongly associated with mortality than anxiety (sTables 7&8).

Examining the Effect of Antidepressant Use on Disease Progression

In ENROLL-HD, 1877 antidepressant-naive participants (who had been previously free of depression and anxiety) experienced a new episode of psychiatric symptoms: 194 were treated with antidepressants (10.33%). The treated group were significantly different from the untreated across a number of variables: the treated group were older, with more advanced disease, higher scores on all psychiatric variables (depression, suicidality, anxiety, irritability), more psychoactive drug use, more frequent antidepressant treatments across the study, more frequent mental health events, but smaller NCAG, after the propensity scoring process the groups only differed on baseline composite score, but this difference did not meet the threshold for significant imbalance in propensity weights [16,17] (Kolmogorov-Smirnov statistic <0.1 and standardised mean difference <0.2; Table 3, Supplementary Table 9).

Participants experiencing psychiatric symptoms who were treated with antidepressants had slower decline in the composite disease score compared to the untreated group (Figure 2a, Supplementary Table 10); per year, the composite disease score declined by 0.89 in this group, antidepressants lessened this decline by 0.36 (95%CI 0.13,0.6;p=0.002). Similarly, the effect of antidepressant exposure (duration of antidepressant treatment) slowed composite disease score decline: 1 years treatment with an antidepressant slowed the annual composite disease score change by 0.06 (6.7%/year)(95%CIs 0.059,0.061;p=0.044)(Figure 2b, Supplementary Table 11).

Examining the Effects of Antidepressant Use on Mortality

Mortality rates were similar between the treated and untreated groups(7.2%), but time to death was much longer in the treated group compared to the untreated(1180.93 vs 700.79 days)(Supplementary Table 12). Fitting a Cox proportional hazards model showed that this difference was significant: antidepressant use was associated with reduced all cause mortality risk(HR 0.38,p=0.04)(Figure 4, Supplementary Table 13). This effect was not driven by a reduction in suicide rate (Supplementary Table 14&15). The association between antidepressants and reduction in mortality was also seen with antidepressant exposure (HR 0.66,p=0.043)(Supplementary Table 16).

Effect of Antidepressant Class on Disease Progression and Mortality

As an exploratory analysis, we looked at the effect of individual antidepressant classes on disease progression in the ENROLL-HD data. We separated antidepressants into tricyclic antidepressants (TCAs), serotonin noradrenaline reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs) and atypical agents. The majority of study participants received SSRIs (Supplementary Table 17), with relatively small numbers receiving TCAs (n=13). We did not find any individual class effect on composite disease score progression. However there were significant effects on mortality. Both atypical agents (HR 0.19,p=0.028) and TCAs (HR $1.7x10^{-5}$,$p<2x10^{-16}$) reduced all cause mortality (Figure 4, Supplementary Table 4b) compared to no treatment. However the effects on suicide and non-suicide mortality risk differed: TCAs reduced suicide and non-suicide mortality risk; SSRIs and atypical agents reduced suicide risk alone, whilst SNRIs affected non-suicide mortality only (sTables 18-20). As antidepressant class prescribing patterns vary by region[18], we created a model also including geographical region (Supplementary Table 21), but this did not change the effect of antidepressant classes on mortality.

Sensitivity Analysis

A tipping point analysis (Supplementary Fig. 1) of outcome and independent variable showed that, for an unmeasured confounder to eliminate the association between composite disease score and antidepressants, the strength of the association between exposure and outcome would need to be larger than any variable in the model, and, in particular, would need to be twice the size of baseline composite score. A sensitivity analysis for an association between an unknown confounder added to the model and the outcome,

showed that such a confounder added to the model that accounted for more than 4.98% of the residual variation in composite disease score would eliminate the effect of antidepressant treatment on rate of change of the composite disease score. This is less than the effect of baseline composite disease score and time, but more than comorbidities, psychiatric scores, NCAG, age, sex, history of addiction, antidepressant burden and previous mental health events (Supplementary Table 22).

Sequential hotdeck imputation of missing data did not change the association between antidepressant treatment and composite score (Supplementary Table 23). Nor did hotdeck imputation of all variables in the model change the propensity scoring outcome for the mortality analysis.

Discussion

In this work, we have shown that in HD participants with new episodes of depression or anxiety, antidepressant initiation reduces mortality risk, and slows disease progression. An exploratory analysis suggests the relationship between antidepressants and mortality is not explained by a reduction in suicide risk. As psychiatric symptoms are common in neurodegenerative diseases more widely, the effect of antidepressants on disease progression in these disorders merits further study. Significantly, we have also shown that in HD, psychiatric symptoms are associated with faster disease progression, and increased mortality.

Previous work in the ENROLL-HD dataset, had suggested more rapid disease progression in patients treated with antidepressants[7]. However, the model in this study did not include relevant mental health variables, and did not select participants experiencing incident mental health problems introducing confounding by indication. More recently a propensity score approach was used in motor-symptomatic participants in ENROLL-HD[19]. This study included depression and anxiety scores, NCAG, composite disease score components in the model, with a primary outcome of depression score at first follow up visit after initiation. They found 86 new users of antidepressants, but did not find differences at first follow-up on depression or any measure of disease progression. We looked at disease progression over time, included a substantially larger N and found an association both with disease progression and a reduction in all cause mortality risk. A number of studies have also noted an association between antidepressant use and the onset of cognitive decline or diagnosis

of dementia[20,21], though these studies were not able to account for baseline psychiatric symptom severity. More recent observational work in Alzheimer's has shown an association between tricyclic antidepressants (but not other antidepressants) and worsening cognitive decline, but no association with imaging biomarkers of disease progression[22]. In Parkinson's disease (PD), antidepressants were initially linked with a higher risk of disease onset in an observational study[23], although animal work in PD models has shown beneficial effects of antidepressant treatment on alpha synuclein deposition[24], and a trial of antidepressants for depression in PD has included disease progression as a secondary outcome[25].

To date, no clinical trial of antidepressants in HD (for any indication) has included more than 30 participants in each arm and the follow-up has been limited to several months. Randomised controlled trials (summarised in Zadegan et al[26]) of fluoxetine (primary outcome – function, measured by the TFC), citalopram (primary outcome – cognition), bupropion (primary outcome – apathy) and a novel agent PNU-96391A (primary outcome – safety and tolerability) all had follow-up periods shorter than 6 months and 20 or fewer participants in each arm. None showed any benefit on established clinical measures of disease progression, but previous work in HD has shown the need for a substantially larger sample size and longer follow-up[11].

The association between psychiatric symptoms and disease progression in HD suggests that there may be an additional mechanism leading to disease progression other than that driven by increasing NCAG, represented phenotypically by psychiatric symptomatology. As psychiatric symptoms are more frequent in many neurodegenerative diseases compared to the wider population, this raises the intriguing possibility that there is a common mechanism underlying these symptoms across neurodegenerative diseases, potentially opening novel therapeutic avenues. Determining what this process might be is difficult as the mechanism(s) leading to depression are uncertain. Previous work by our group has shown overlap with genetic risk for psychiatric disorders in neurodegenerative disease and the general population[27,28]. Impairments in neurogenesis have been found in patients with depression in the general population, are known to be rescued by antidepressant treatment, and have been found in R6/1 animal models of HD that can be rescued by fluoxetine treatment[29]. Hypothalamo-pituitary axis dysfunction has been found in depression in the general population and HD[30]. Evidence of CNS inflammation has been found in depression[31], and also in HD - with some data to suggest modification in imaging biomarkers of disease progression with immunomodulatory treatment[32].

A strength of our approach has been to address confounding by indication: study participants with more severe symptoms necessitating symptomatic treatment may have worse underlying disease and consequently a higher risk of death. Hence symptomatic treatment initiation (e.g. starting an antidepressant) may be a marker of more rapid disease progression rather than a cause of more rapid disease progression. We were able to determine symptoms associated with antidepressant initiation and then compare subsequent disease progression and mortality. Confounding by indication is a significant limitation in previous analyses of psychotropic drug use in dementia and other neurodegenerative diseases. Hence conflicting results have been seen from large population analyses. For example Mo et al[33], and others[34] have found higher mortality in patients with dementia receiving antidepressants, but others have shown a reduced risk[35,36]. Similarly in Parkinson's disease, evidence of both increased and reduced risk of mortality with antidepressant use has been found[37,38].

We found differential effects of antidepressant classes on mortality: TCAs were associated with reductions in both suicide and non-suicide related mortality, atypical agents and SSRIs with reduced suicide risk; whilst SNRIs were associated with reductions in non-suicide related mortality. Previous work by our group[39] has suggested that atypical agents and SSRIs have a greater effect on depression in HD than do other antidepressant classes, which may reflect their effect on suicide rates. The effect of SNRIs and TCAs on non-suicide mortality are more difficult to explain, although data from Parkinson's disease suggests that nortriptyline in particular may delay disease progression[40].

There are a number of limitations in this study. Propensity score matching is not able to account for unobserved confounders, however there is some evidence to suggest that observed and unobserved confounders co-vary[41]. Further to this, several recent studies have shown that propensity scoring in observational data replicates the significance and effect sizes reported in randomised controlled trials[42,43]. Our sensitivity analyses suggested that unobserved or mediating variables would need to be as large or larger than time or baseline composite disease score to influence the results which seems improbable. We used two scales to determine presence/absence of depression or anxiety, as it is not clear which scale is more reliable in pwHD, and the correlation between the scales although significant was only moderate (0.43). The NCAG was slightly shorter in the antidepressant-treated group, despite this group being at a more advanced disease stage on the composite disease score.

Previous work suggests psychiatric symptoms may be even more prevalent in individuals with shorter (and even intermediate) NCAG, which may explain this finding[44]. The effects of antidepressant classes on all cause mortality risk should be interpreted with a degree of caution, as the numbers in some groups were small.

In conclusion, in this work we have shown reduced mortality risk and slower disease progression on clinical, imaging biomarker and fluid biomarkers in HD patients treated with antidepressants compared to untreated patients. This finding may be of wider applicability to other neurodegenerative diseases, and raises the possibility of a second mechanism contributing to disease progression in HD.

Data availability

Data from ENROLL-HD is available following completion of a specific data request to CHDI as data controllers (https://www.enroll-hd.org/for-researchers/access-data-biosamples/).

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Competing interests

Dr McLauchlan reports no conflict of interest, Dr Drew has received financial honoraria for reviewing clinical trial protocols as part of the Enroll-HD clinical trials committee, Professor Holmans is paid an honorarium of $2000 per annum as part of the scientific review committee, Professor Rosser is a leadership team member for Prilenia Proof-HD study (paid to Cardiff University), consultancy for Teitur Trophics (Paid to Cardiff University), sits on the advisory board of Sana Biotech; Human embryonic stem cell-derived glial progenitor cells

(Other Name(s): Glial progenitor cells, SC379), and has served on ad hoc advisory boards for Alchemab, Alnylam, UniQure, Roche, WAVE, and Novartis.

Supplementary material

Supplementary material is available at *Brain* online.

References

1. McColgan P, Tabrizi SJ. Huntington's disease: a clinical review. *Eur J Neurol*. 25:24-34.

2. van Duijn E, Craufurd D, Hubers AM, et al. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY. *J Neurol Neurosurg Psychiatry*. 2014;85:1411-1418.

3. Ho AK, Gilbert AS, Mason SL, Goodman AO, Barker RA. Health-related quality of life in Huntington's disease: Which factors matter most? *Mov Disord J Mov Disord Soc*. 2009;24:574-578.

4. Andriessen RL, Oosterloo M, Hollands A, Linden DEJ, de Greef BTA, Leentjens AFG. Psychotropic medication use in Huntington's disease: A retrospective cohort study. *Parkinsonism Relat Disord*. 2022;105:69-74. doi:10.1016/j.parkreldis.2022.11.004

5. Dudas R, Malouf R, McCleery J, Dening T. Antidepressants for treating depression in dementia [Internet. *Cochrane Database Syst Rev*. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003944.pub2/information

6. Phiri P, Engelthaler T, Carr H, Delanerolle G, Holmes C, Rathod S. Associated mortality risk of atypical antipsychotic medication in individuals with dementia. *World J Psychiatry*. 2022;12(2):298-307. doi:10.5498/wjp.v12.i2.298

7. Griffin BA, Booth MS, Busse M, et al. Estimating the causal effects of modifiable, non-genetic factors on Huntington Disease progression using propensity score weighting. *Parkinsonism Relat Disord*. 2021;83:56. doi:10.1016/j.parkreldis.2021.01.010

8. Landwehrmeyer GB, Fitzer-Attas CJ, Giuliano JD. Data Analytics from Enroll-HD, a Global Clinical Research Platform for Huntington's Disease. *Mov Disord Clin Pr*. (wn];4(2):212–224).

9. de Sousa J, Jones LA, Rickards H. Validation of self-report depression rating scales in Huntington's disease. *Mov Disord J Mov Disord Soc*. 2010;25:91-96.

10. Callaghan J, Stopford C, Arran N, Boisse MF, Coleman A, Santos RD. Reliability and Factor Structure of the Short Problem Behaviors Assessment for Huntington's Disease (PBA-s) in the TRACK-HD and REGISTRY studies. *J Neuropsychiatry Clin Neurosci*. 2015;27:59-64.

11. Schobel SA, Palermo G, Auinger P. Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. *Neurology*. 2017;89(24):2495-2502.

12. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. *Mov Disord*. 1996;11:136-142.

13. Funk MJ, Westreich D, Wiesen C, Stürmer T, Brookhart MA, Davidian M. Doubly Robust Estimation of Causal Effects. *Am J Epidemiol*. 2011;173(7):761-767. doi:10.1093/aje/kwq439

14. D'Agostino McGowan L. Sensitivity Analyses for Unmeasured Confounders. *Curr Epidemiol Rep*. 2022;9(4):361-375. doi:10.1007/s40471-022-00308-6

15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71

16. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107. doi:10.1002/sim.3697

17. Griffin BA, Schuler MS, Cefalu M, et al. A tutorial for propensity score weighting for moderation analysis with categorical variables: An application examining smoking disparities among sexual minority adults. *Med Care*. 2023;61(12):836-845. doi:10.1097/MLR.0000000000001922

18. McLauchlan D, Drew C, Holmans P, Rosser A. Antidepressant Treatment in Huntington's Disease: Regional and Case-Control Variation. *medRxiv*. Preprint posted online August 5, 2025:2025.08.01.25332817. doi:10.1101/2025.08.01.25332817

19. Ogilvie AC, Carnahan RM, Chrischilles EA, Schultz JL. The effects of antidepressants on depressive symptoms in manifest Huntington's disease. *J Psychosom Res*. 2022;162:111023. doi:10.1016/j.jpsychores.2022.111023

20. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med*. 2015;175(3). doi:10.1001/jamainternmed.2014.7663

21. Wang C, Gao S, Hendrie HC, et al. Antidepressant Use in the Elderly Is Associated With an Increased Risk of Dementia. *Alzheimer Dis Assoc Disord*. 2016;30(2):99-104. doi:10.1097/WAD.0000000000000103

22. vom Hofe I, Stricker BH, Vernooij MW, Ikram MK, Ikram MA, Wolters FJ. Antidepressant use in relation to dementia risk, cognitive decline, and brain atrophy. *Alzheimers Dement*. 2024;20(5):3378-3387. doi:10.1002/alz.13807

23. Alonso A, Rodríguez LAG, Logroscino G, Hernán MA. Use of antidepressants and the risk of Parkinson's disease: a prospective study. *J Neurol Neurosurg Psychiatry*. 2009;80(6):671-674. doi:10.1136/jnnp.2008.152983

24. Collier TJ, Srivastava KR, Justman C, et al. Nortriptyline inhibits aggregation and neurotoxicity of alpha-synuclein by enhancing reconfiguration of the monomeric form. *Neurobiol Dis*. 2017;106. doi:10.1016/j.nbd.2017.07.007

25. Schrag A, Carroll C, Duncan G, et al. Antidepressants Trial in Parkinson's Disease (ADepT-PD): protocol for a randomised placebo-controlled trial on the effectiveness of escitalopram and nortriptyline on depressive symptoms in Parkinson's disease. *BMC Neurol*. 2022;22(1):474. doi:10.1186/s12883-022-02988-5

26. Zadegan SA, Ramirez F, Reddy KS, et al. Treatment of Depression in Huntington's Disease: A Systematic Review. *J Neuropsychiatry Clin Neurosci*. Published online March 26, 2024:appineuropsych20230120. doi:10.1176/appi.neuropsych.20230120

27. Hollingworth P, Sweet R, Sims R, et al. Genome-wide association study of Alzheimer's disease with psychotic symptoms. *Mol Psychiatry*. 2012;17(12):1316-1327. doi:10.1038/mp.2011.125

28. Ellis N, Tee A, McAllister B, et al. Genetic Risk Underlying Psychiatric and Cognitive Symptoms in Huntington's Disease. *Biol Psychiatry*. 2020;87(9):857-865. doi:10.1016/j.biopsych.2019.12.010

29. Grote HE, Bull ND, Howard ML, et al. Cognitive disorders and neurogenesis deficits in Huntington's disease mice are rescued by fluoxetine. *Eur J Neurosci*. 2005;22(8):2081-2088. doi:10.1111/j.1460-9568.2005.04365.x

30. Hubers A a. M, van der Mast RC, Pereira AM, et al. Hypothalamic-Pituitary-Adrenal Axis Functioning in Huntington's Disease and its Association with Depressive Symptoms and Suicidality. *J Neuroendocrinol*. 2015;27(3):234-244. doi:10.1111/jne.12255

31. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD. Inflammation Causes Mood Changes Through Alterations in Subgenual Cingulate Activity and Mesolimbic Connectivity. *Biol Psychiatry*. 2009;66(5):407-414. doi:10.1016/j.biopsych.2009.03.015

32. Reilmann R, Anderson KE, Feigin A, et al. Safety and efficacy of laquinimod for Huntington's disease (LEGATO-HD): a multicentre, randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Neurol*. 2024;23(3):243-255. doi:10.1016/S1474-4422(23)00454-4

33. Mo M, Abzhandadze T, Hoang MT, et al. Antidepressant use and cognitive decline in patients with dementia: a national cohort study. *BMC Med*. 2025;23(1):82. doi:10.1186/s12916-025-03851-3

34. Maust DT, Kim HM, Seyfried LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry*. 2015;72(5):438-445. doi:10.1001/jamapsychiatry.2014.3018

35. Su JA, Chang CC, Wang HM, Chen KJ, Yang YH, Lin CY. Antidepressant treatment and mortality risk in patients with dementia and depression: a nationwide population cohort study in Taiwan. *Ther Adv Chronic Dis*. 2019;10:2040622319853719. doi:10.1177/2040622319853719

36. Enache D, Fereshtehnejad SM, Kåreholt I, et al. Antidepressants and mortality risk in a dementia cohort: data from SveDem, the Swedish Dementia Registry. *Acta Psychiatr Scand*. 2016;134(5):430-440. doi:10.1111/acps.12630

37. Orayj K. Impact of Antidepressants on Cardiac Events and All-Cause Mortality in Parkinson's Disease: A National Data-Linkage Study. *Neuropsychiatr Dis Treat*. 2021;17:2499-2510. doi:10.2147/NDT.S325521

38. Frandsen R, Baandrup L, Kjellberg J, Ibsen R, Jennum P. Increased all-cause mortality with psychotropic medication in Parkinson's disease and controls: a national register-based study. *Parkinsonism Relat Disord*. 2014;20(11):1124-1128. doi:10.1016/j.parkreldis.2014.07.012

39. McLauchlan DJ, Lancaster T, Craufurd D, Linden DEJ, Rosser AE. Different depression: motivational anhedonia governs antidepressant efficacy in Huntington's disease. *Brain Commun*. 2022;4(6):fcac278. doi:10.1093/braincomms/fcac278

40. Paumier KL, Siderowf AD, Auinger P, et al. Tricyclic antidepressants delay the need for dopaminergic therapy in early Parkinson's disease. *Mov Disord*. 2012;27(7):880-887. doi:10.1002/mds.24978

41. Austin PC, Mamdani MM, Stukel TA. The use of the propensity score for estimating treatment effects: administrative versus clinical data. *Stat Med*. 2005;24(10):1563-1578.

42. Deng Y, Polley EC, Wallach JD, et al. Emulating the GRADE trial using real world data: retrospective comparative effectiveness study. *BMJ*. 2022;379:e070717. doi:10.1136/bmj-2022-070717

43. Moneer O, Daly G, Skydel JJ, et al. Agreement of treatment effects from observational studies and randomized controlled trials evaluating hydroxychloroquine, lopinavir-ritonavir, or dexamethasone for covid-19: meta-epidemiological study. *BMJ*. 2022;377:e069400. doi:10.1136/bmj-2021-069400

44. Killoran A, Biglan KM, Jankovic J, Eberly S, Kayson E, Oakes D. Characterization of the Huntington intermediate CAG repeat expansion phenotype in PHAROS. *Neurology*. 2013;80:2022-2027.

Figure Legends

Figure 1 PRISMA diagram for sample construction from Enroll-HD. Adapted from Page *et al*.[15] *These study participants were included in the analyses to determine the effect of psychiatric symptoms on disease progression and mortality. People with the repeat expansion for HD (PwHD).

Figure 2 The association between psychiatric symptoms with disease progression and mortality. Scatter plot and Kaplan-Meier plot showing the associations between (A) disease progression and (B) survival of participants experiencing psychiatric symptoms (3131/6166) compared to those not (3035/6166).

Figure 3 The effects of antidepressants on disease progression and mortality. Scatter plot and Kaplan-Meier plot showing the effects on (A) disease progression and (B) survival of untreated participants (1683/1877) compared with antidepressant treatment (194/1877) following propensity score (PS) weighting. Larger circles in 3A denote larger PS weights.

Figure 4 Survival plot comparing antidepressant classes to no treatment. Kaplan-Meier plot showing the effect on survival of untreated participants (*n*=1683) compared with different antidepressant classes following propensity score (PS) weighting. SSRI- Selective Serotonin Reuptake Inhibitor (*n*=106), SNRI- Serotonin Noradrenaline Reuptake Inhibitor (*n*=23), TCA- Tricyclic Antidepressant (*n*=13), Atypical (*n*=52).

Table 1 Indications for Antidepressants

	n	Per cent
Depression	16 405	67.74
Anxiety	3134	12.94
Sleep	2052	8.47
Irritability	990	4.09
Other psychiatric	633	2.61
Pain	323	1.33
Apathy	193	0.80
Systemic illness	184	0.76
Unclear	176	0.73
Motor symptoms of HD	76	0.31
Psychosis	50	0.21

Some prescriptions had multiple indications. HD = Huntington's disease.

Table 2 Demographics Psychiatric Symptoms ENROLL-HD

	Psychiatric Symptoms Present N= 3131/6166	Psychiatric Symptoms Absent N= 3035/6166	p value
Age	47.93 (13.81)	47.37 (14.5)	0.034
Sex, female	55.55%	50.25%	<0.001
Baseline composite disease score	12.2 (5.25)	13.15 (4.84)	<0.001
Baseline PBA depression score	1.21 (1.6)	0.3 (0.72)	<0.001
Baseline PBA irritability score	1.43 (2.26)	0.82 (1.8)	0.01
Baseline PBA anxiety score	1.52 (1.68)	0.4 (0.82)	0.01
Baseline PBA suicidality score	0.06 (0.4)	0.01 (0.15)	<0.001
Number of antidepressant	0.69 (1.05)	0.45 (0.88)	<0.001
Previous mental health event	0.24 (0.43)	0.13 (0.34)	<0.001
History of addiction	0.49 (0.5)	0.46 (0.5)	<0.001
Psychoactive drug	0.4 (0.49)	0.28 (0.45)	<0.001
NCAG	43.29 (3.45)	43.14 (3.64)	0.1
Comorbidities	0.26 (0.44)	0.18 (0.38)	<0.001

Data are presented as mean (standard deviation). NCAG = number of CAG repeats; PBA = Problem Behaviours Assessment.

Table 3 Demographics Antidepressant Treatment ENROLL-HD

	Antidepressant treatment N= 194/1877	Control N= 1683/1877	Unweighted p value
Age	52.13 (11.77)	49.91 (13.62)	<0.001
Sex, female	0.57 (0.49)	0.55 (0.50)	0.25
Baseline composite disease score	10.77 (5.11)	11.06 (5.70)	0.16
Baseline PBA depression score	4.43 (3.79)	3.55 (3.50)	<0.001
Baseline PBA irritability score	3.15 (3.25)	2.83 (3.25)	0.01
Baseline PBA anxiety score	5.89 (3.97)	5.50 (3.64)	0.01
Baseline PBA suicidality score	0.86 (2.37)	0.34 (1.35)	<0.001
Number of antidepressants	2.78 (1.81)	0.79 (1.29)	<0.001
Previous mental health event	0.52 (0.50)	0.32 (0.47)	<0.001
History of addiction	0.57 (0.49)	0.55 (0.50)	0.16
Psychoactive drug	0.76 (0.43)	0.53 (0.50)	<0.001
NCAG	43.08 (2.60)	43.37 (3.35)	0.01
Comorbidities	0.41 (0.49)	0.32 (0.47)	<0.001

Data are presented as mean (standard deviation). NCAG = number of CAG repeats; PBA = Problem Behaviours Assessment.

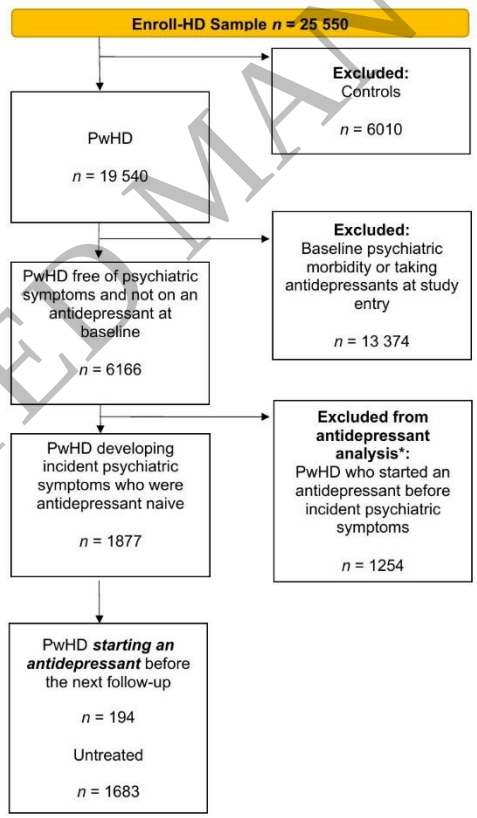

Figure 1

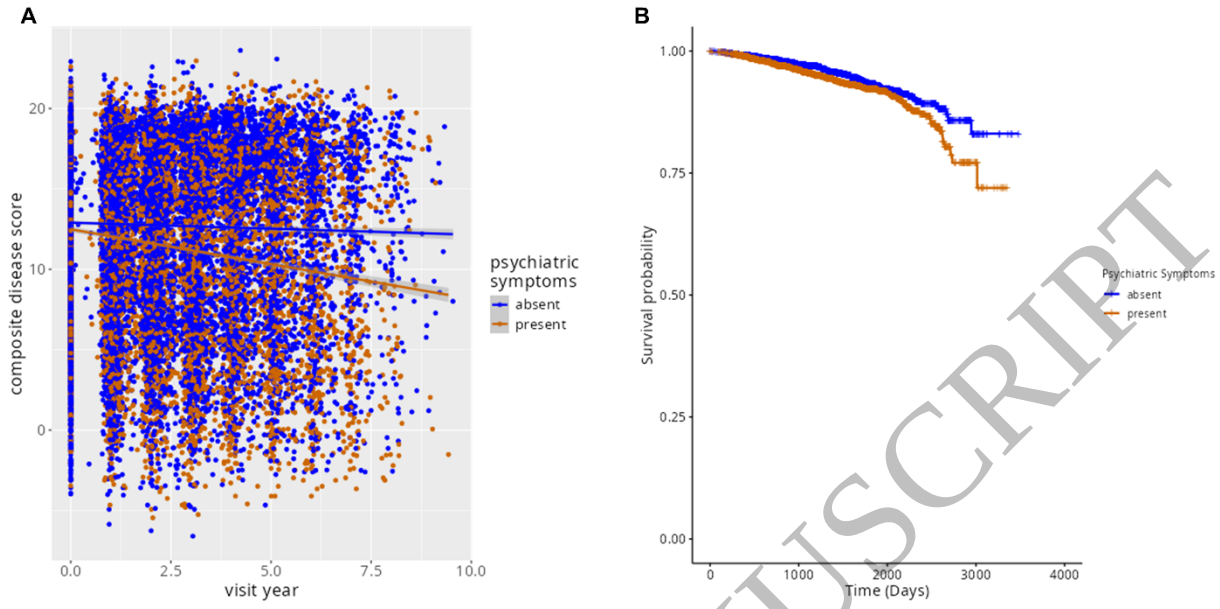

Figure 2
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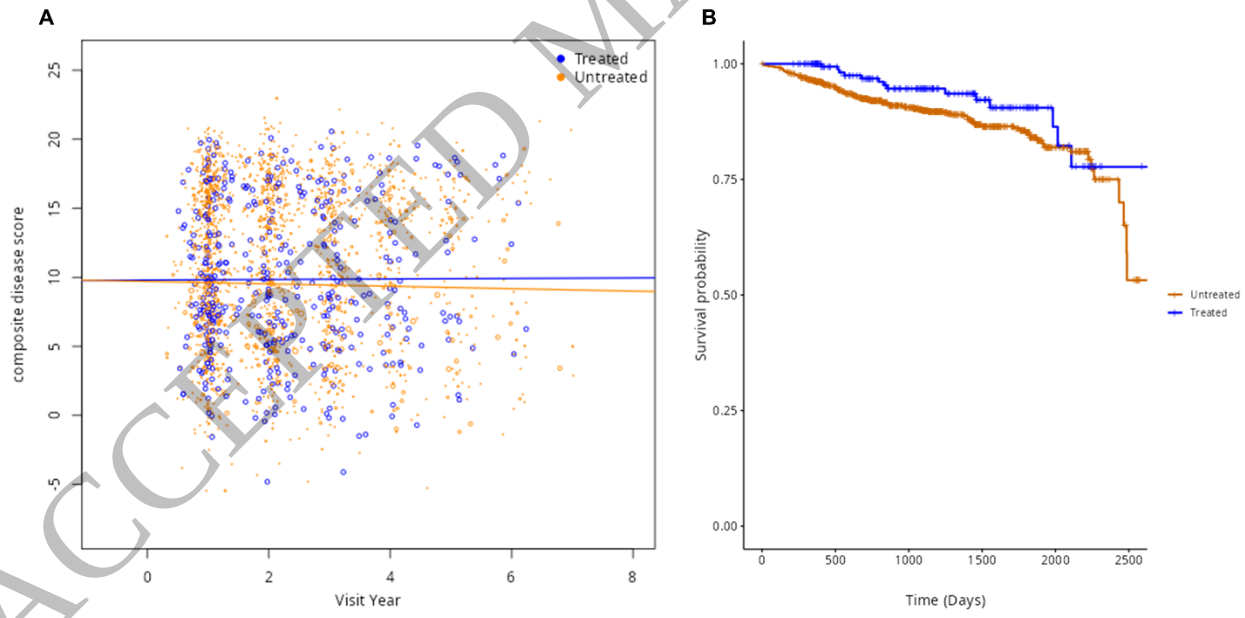

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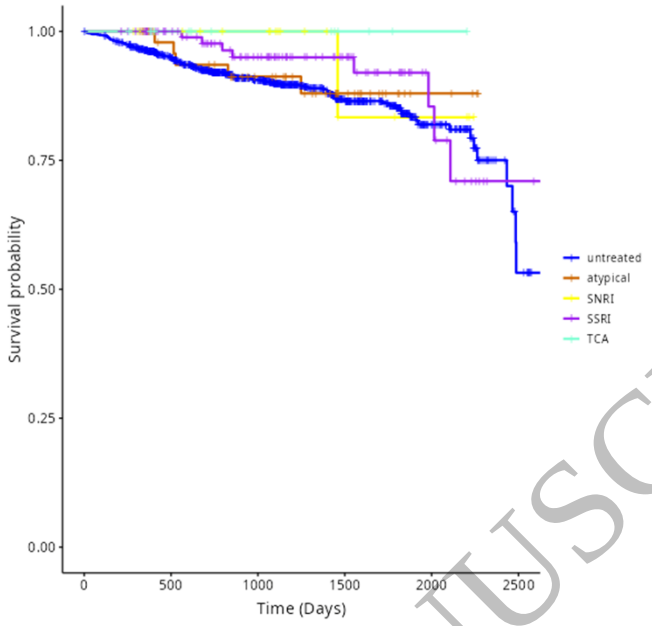

Figure 4
89x87 mm (x DPI)