SECTION EDITOR: IRA SHOULSON, MD

A Randomized, Double-blind, Placebo-Controlled Study of Latrepirdine in Patients With Mild to Moderate Huntington Disease

*HORIZON Investigators of the Huntington Study Group and European Huntington's Disease Network**

Background: Latrepirdine is an orally administered experimental small molecule that was initially developed as an antihistamine and subsequently was shown to stabilize mitochondrial membranes and function, which might be impaired in Huntington disease.

Objective: To determine the effect of latrepirdine on cognition and global function in patients with mild to moderate Huntington disease.

Design: Randomized, double-blind, placebo-controlled study.

Setting: Sixty-four research centers in Australia, Europe, and North America.

Patients: Four hundred three patients with mild to moderate Huntington disease and baseline cognitive impairment (Mini-Mental State Examination score, 10-26).

Intervention: Latrepirdine (20 mg) vs matching placebo administered orally 3 times daily for 26 weeks.

Main Outcome Measures: The co-primary outcome measures were cognition as measured by the change in Mini-Mental State Examination score from baseline to week 26 and global function at week 26 as measured by the Clinician Interview–Based Impression of Change, plus carer interview, which ranges from 1 (marked improvement) to 7 (marked worsening). Secondary efficacy outcome measures included behavior, daily function, motor function, and safety.

Results: The mean change in Mini-Mental State Examination score among participants randomized to latrepirdine (1.5-point improvement) did not differ significantly from that among participants randomized to placebo (1.3-point improvement) ($P=.39$). Similarly, the distribution of the Clinician Interview–Based Impression of Change, plus carer interview did not differ significantly among those randomized to latrepirdine compared with placebo ($P=.84$). No significant treatment effects were detected on the secondary efficacy outcome measures. The incidence of adverse events was similar between those randomized to latrepirdine (68.5%) and placebo (68.0%).

Conclusion: In patients with mild to moderate Huntington disease and cognitive impairment, treatment with latrepirdine for 6 months was safe and well tolerated but did not improve cognition or global function relative to placebo.

Trial Registration: clinicaltrials.gov Identifier: NCT00920946

JAMA Neurol. 2013;70(1):25-33. Published online October 29, 2012. doi:10.1001/2013.jamaneurol.382

*The authors for the HORIZON Investigators of the Huntington Study Group and European Huntington's Disease Network are listed at the end of the article. The authors are indicated in the "Group Information" subsection of the "Acknowledgment" section by an asterisk following their name.

HUNTINGTON DISEASE (HD) is an autosomal dominant neurodegenerative disorder that is characterized by involuntary movements, behavioral disorders, and cognitive dysfunction. The symptoms typically begin in the fourth decade of life and lead to progressive deterioration in functional capacity and independence.[1] Current treatment is symptomatic, but no treatments are available for the cognitive dysfunction in HD.[2]

Latrepirdine is an orally administered experimental small molecule that was initially developed as an antihistamine and subsequently was shown to stabilize mitochondrial membranes and function,[2-5] which might be impaired in HD.[6,7] In a previous randomized trial[8] of latrepirdine in 91 individuals with mild to moderate HD, latrepirdine was found to be safe and well tolerated during 90 days of treatment. In addition, compared with placebo, latrepirdine treatment was associated with a mean 0.97-point improvement in the Mini-

Corrected on January 11, 2013

Mental State Examination (MMSE) score but not with improvement in other cognitive outcome measures. Based on the results of this phase 2 study, we conducted an international, multicenter, randomized, double-blind, placebo-controlled study of latrepirdine to assess its efficacy in improving cognition and global function in patients with mild to moderate HD.

METHODS

STUDY ORGANIZATION AND DESIGN

The multicenter clinical trial was organized and conducted by the Huntington Study Group and the European Huntington's Disease Network.

We conducted a randomized, double-blind, placebo-controlled, parallel-group trial of latrepirdine (20 mg) vs matching placebo administered orally 3 times daily for 26 weeks. The protocol and consent forms were approved by the University of Rochester (Rochester, New York) institutional review board and by the institutional review board at each participating site.

Eligible study participants provided written consent. After eligibility for the study was confirmed, participants were randomized in a 1:1 ratio to latrepirdine or placebo according to a computer-generated permuted block randomization schedule that was stratified by site and by concomitant use of tetrabenazine. Blinded treatment assignment was provided by an independent interactive web and voice recognition service. Individuals randomized to latrepirdine received latrepirdine (10 mg) 3 times daily for the first 7 days, followed by latrepirdine (20 mg) 3 times daily for the remainder of the treatment period. Participants, investigators, and sponsors were masked to study group assignment.

After a screening visit to determine eligibility, a baseline visit was conducted within 32 days of screening, followed by in-person visits at weeks 2, 6, 13, 18, and 26 after baseline. A telephone safety assessment was performed 4 to 8 days after the baseline visit, and a follow-up visit was conducted at week 30 (4 weeks after the last administration of study drug) to assess safety in participants who did not choose to enroll in an open-label extension study of latrepirdine immediately following the week 26 visit.

STUDY PARTICIPANTS

Study participants were recruited from 64 research centers in Australia (n=3), Europe (n=28), and North America (n=33). Eligible participants were at least 30 years old, had clinical features of mild to moderate HD based on a Unified Huntington's Disease Rating Scale[9] total functional capacity of 5 to 13, and had a trinucleotide (cytosine-adenine-guanine) repeat length of 36 or greater in the huntingtin gene by direct DNA testing.[10] Participants had to have subjective evidence of cognitive impairment as assessed by the site investigator and an MMSE score of 10 to 26 at both the screening and baseline visits (before study drug administration). Participants were ambulatory, did not require skilled nursing care at baseline, and agreed to use adequate birth control or were not of reproductive potential. Individuals taking antidepressants, neuroleptics, or tetrabenazine had to be receiving stable dosages before randomization. All the participants had to have a caregiver who assisted or spent time with the individual at least 5 days per week for at least 3 hours per day and who was willing to provide input on outcome measures.

Excluded from the study were individuals who had active suicidal ideation or any major medical illness that would interfere with their ability to complete the study procedures, including diabetes mellitus requiring treatment with insulin or a history of cancer within 5 years (excluding stable prostate cancer or nonmelanoma skin cancer). Individuals with active cardiovascular disease, bradycardia (heart rate, <45 beats/min), significant electrocardiographic abnormalities, hypotension (systolic blood pressure, <86 mm Hg), or uncontrolled hypertension (successive blood pressures, >170/105 mm Hg) were also excluded. Additional exclusionary criteria were significant laboratory abnormalities, significant use of narcotic analgesics, a history of human immunodeficiency virus, a history of seizures requiring ongoing treatment, a history of other diseases known to affect cognition (eg, significant traumatic brain injury or dementing illnesses other than HD), and recent use of clozapine, memantine hydrochloride, bupropion hydrochloride, a cholinesterase inhibitor, or a nonselective antihistamine.

OUTCOME MEASURES

The study had 2 co-primary outcome measures. The first was the change from baseline to week 26 in cognition as measured by the MMSE.[11,12] The second was the change in global function at week 26 as measured by the Clinician Interview–Based Impression of Change, plus carer interview (CIBIC-Plus).[13] The MMSE score was selected as a co-primary outcome measure because of its frequent use in dementia trials,[14-16] its gradual decline in HD,[17] and its signal of benefit in previous trials involving latrepirdine.[8,18] The CIBIC-Plus, which is widely used in dementia trials,[13] was used as a co-primary outcome measure to provide a global assessment of function and to support the clinical relevance of a treatment effect on the MMSE score. The CIBIC-Plus comprises Likert-type scales for disease severity and change from baseline based on semistructured interviews of the research participant and the caregiver.[19] The site investigator conducted the MMSE at the screening, at baseline, and at visits at weeks 6, 13, and 26. A separate, independent rater, blinded to other aspects of the study, conducted the semistructured interviews at baseline, at week 13, and at week 26. Secondary efficacy outcome measures included changes from baseline to week 26 in behavior as measured by the Neuropsychiatric Inventory,[19-21] activities of daily living as measured by the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale,[22] and motor function as measured by the Unified Huntington's Disease Rating Scale total motor score.[9]

Safety was addressed at all the study visits and included assessment of adverse events, evaluation of suicidality using the Columbia Classification Algorithm of Suicide Assessment,[23] and review of vital signs, electrocardiographic reading, concomitant medication use, and laboratory test results, including serum chemistry levels, hematology, and urinalysis. The safety of participants was gauged by a clinical monitor from the sponsor, by the Huntington Study Group, and by an independent data monitoring committee that reviewed safety data and had access to treatment assignments.

STATISTICAL ANALYSIS

The primary statistical analyses were performed in accord with a modified version of the intent-to-treat principle. For each of the co-primary outcome measures, participants who did not have at least 1 postbaseline value were excluded from the analysis of that outcome variable. The change in MMSE score from baseline to week 26 was analyzed using a mixed-model repeated-measures approach.[24] As independent variables, the model included treatment group, baseline MMSE score, tetrabenazine use (yes or no), region (Australia or North America vs Eu-

rope), and week (6, 13, and 26, treated as a categorical variable), as well as the interaction between treatment group and week. The covariance matrix for the within-subject measurements was specified as unstructured for model fitting. This approach appropriately accounts for missing data when estimating the model parameters under the "missing at random" assumption.[25] The treatment effect at week 26 (difference in adjusted mean response between the latrepirdine and placebo groups), with corresponding 95% CI and *P* value, was estimated using this model.

For the CIBIC-Plus at week 26, the distribution of responses was compared between the latrepirdine and placebo groups using a stratified Cochran-Mantel-Haenszel mean score test[26] using equally spaced scores for the categories of marked improvement, moderate improvement, minimal improvement, no change, minimal worsening, moderate worsening, and marked worsening, along with stratification factors that included tetrabenazine use and the baseline Clinician Interview–Based Impression of Severity score, categorized as 1 to 3 (normal to mildly ill), 4 (moderately ill), or 5 to 7 (markedly ill to extremely ill). For the analyses of the CIBIC-Plus, missing values were imputed by carrying forward the last available postbaseline observation. For a beneficial effect of latrepirdine to be declared, the treatment effects on both the change in MMSE score and the CIBIC-Plus at week 26 were required to be statistically significant at the 5% level (2-tailed) in favor of latrepirdine.

The mixed-model repeated-measures analyses were applied to secondary efficacy outcomes, as well as changes from baseline in continuous safety outcomes (vital signs, laboratory test results, and electrocardiographic reading). Adverse events were summarized as the percentage of participants in each treatment group who experienced the event at least once during the trial.

The intended sample size for the study was 350 study participants (175 per treatment group). Assuming an SD of 3.2 for the change in MMSE score, an SD of 1.2 for the CIBIC-Plus, and a 10% dropout rate, this sample size provided approximately 99% power to detect a 1.6-point difference in the mean response between the latrepirdine and placebo groups on the MMSE and approximately 84% power to detect a 0.4-point difference in the mean response on the CIBIC-Plus using a 5% significance level (2-tailed). Therefore, the overall power to detect treatment effects on both outcome variables was at least 83%, assuming a nonnegative correlation between these variables.

RESULTS

STUDY PARTICIPANTS

From July 9, 2009, to July 10, 2010, a total of 519 individuals were screened, and 403 participants were randomized to the study arms (**Figure 1**). Failing to meet inclusion criteria (n=56) was the most common reason for exclusion, with another 52 individuals failing to meet MMSE enrollment criteria. Data from 396 of 403 participants (98.3%) were included in the primary analyses of the MMSE; 7 participants did not have a postbaseline MMSE evaluation. Data from 393 of 403 participants (97.5%) were included in the primary analyses of the CIBIC-Plus; 10 participants did not have a postbaseline CIBIC-Plus evaluation. Data from all 403 participants were included in the safety analyses. The baseline demographic and clinical characteristics of the study participants randomized to latrepirdine (n=200) and placebo (n=203) were similar (**Table 1**).

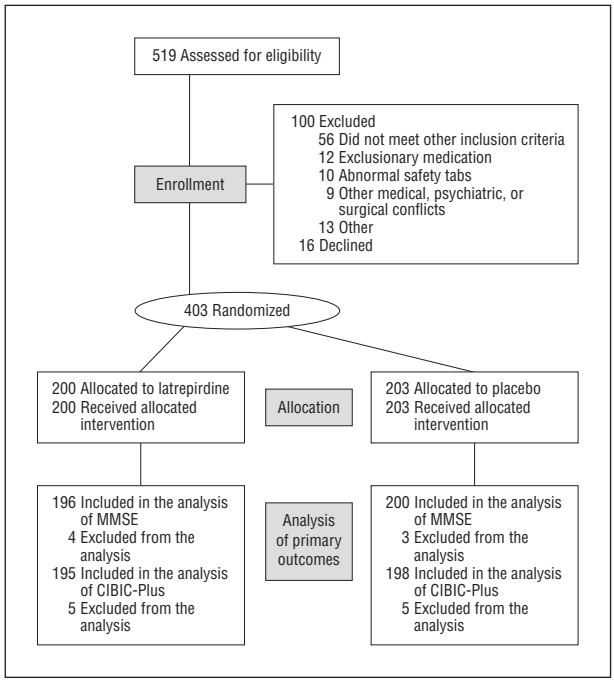

Figure 1. Participant flow. CIBIC-Plus indicates Clinician Interview–Based Impression of Change, plus carer interview; MMSE, Mini-Mental State Examination.

EFFICACY

The mean change in the MMSE score from baseline to week 26 was not significantly different for those randomized to latrepirdine (1.5-point improvement) compared with those randomized to placebo (1.3-point improvement) (*P* = .39) (**Table 2**). In both groups, the mean MMSE scores significantly improved from baseline during the course of the study (**Figure 2**), but no significant difference between groups was observed at any time point. Exploratory analyses found that the effect of latrepirdine did not depend on age, sex, years of education, tetrabenazine use, region, or baseline MMSE score. Similarly, the distribution of the CIBIC-Plus did not differ significantly between the groups at week 26 (*P* = .84), with most participants demonstrating minimal change, if any, during the treatment period (**Table 3**). No significant differences between groups were observed in the secondary efficacy outcome measures assessing behavior, motor function, or activities of daily living (Table 2). Medication compliance, as measured by the percentage of study medication that was taken on schedule, was on average greater than 95% in both treatment groups.

SAFETY

Latrepirdine was well tolerated in the study, with 93.5% of research participants randomized to latrepirdine completing the 6-month study compared with 91.6% of research participants randomized to placebo (Figure 1). During the study, 10% of those receiving latrepirdine had their study medication temporarily suspended because of an

Table 1. Baseline Demographic and Clinical Characteristics of the Study Participants

Characteristic	Latrepirdine Group (n = 200)	Placebo Group (n = 203)
Age, mean (SD), y	53.3 (9.7)	51.6 (10.2)
Female sex, No. (%)	110 (55.0)	100 (49.3)
Race/ethnicity, No. (%)		
White	195 (97.5)	193 (95.1)
Black	2 (1.0)	4 (2.0)
Other	1 (0.5)	4 (2.0)
Not reported	2 (1.0)	2 (1.0)
Education, mean (SD), y	13.1 (3.1)	13.1 (3.0)
Region, No. (%)		
North America	71 (35.5)	73 (36.0)
Europe	121 (60.5)	123 (60.6)
Australia	8 (4.0)	7 (3.4)
Time since diagnosis, mean (SD), y	4.4 (3.6)	4.4 (3.5)
Tetrabenazine use, No. (%)	32 (16.0)	31 (15.3)
Baseline MMSE score, mean (SD)	22.6 (3.0)	22.2 (2.8)
Clinician Interview–Based Impression of Severity, No. (%)		
Normal	0	0
Borderline ill	6 (3.0)	5 (2.5)
Mildly ill	51 (25.5)	56 (27.6)
Moderately ill	97 (48.5)	96 (47.3)
Markedly ill	38 (19.0)	35 (17.2)
Severely ill	8 (4.0)	11 (5.4)
Extremely ill	0	0
Neuropsychiatric Inventory total score, mean (SD)	9.3 (9.9)	8.4 (8.6)
Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale total score, mean (SD)	59.6 (14.1)	59.3 (14.4)
Unified Huntington's Disease Rating Scale, mean (SD)		
Total functional capacity	7.5 (2.1)	7.6 (2.0)
Total motor score	41.9 (16.1)	42.0 (17.0)

Abbreviation: MMSE, Mini-Mental State Examination.

Table 2. Treatment Effects on Efficacy Outcomes at Week 26[a]

Outcome Variable	Mean Change		Treatment Effect (95% CI)	*P* Value
	Latrepirdine Group	Placebo Group		
Co-primary outcome measure				
MMSE score	1.5	1.3	0.2 (–0.3 to 0.7)	.39
Secondary efficacy outcome measures				
Neuropsychiatric Inventory total score	–1.6	–1.7	0.2 (–1.2 to 1.6)	.82
Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale total score	–1.8	–0.8	–0.9 (–2.6 to 0.8)	.28
Unified Huntington's Disease Rating Scale total motor score	1.8	1.5	0.3 (–1.4 to 2.1)	.72

Abbreviation: MMSE, Mini-Mental State Examination.
[a]The mean changes and treatment effects are estimated using a repeated-measures analysis of covariance model with week, region, treatment group, baseline MMSE score, tetrabenazine use, and the interaction between week and treatment group. See the "Statistical Analysis" subsection for details.

adverse event compared with 5% of those receiving placebo.

In the clinical trial, 21 participants (9 randomized to latrepirdine and 12 randomized to placebo) experienced a serious adverse event. One death occurred during the study in a 56-year-old woman who was randomized to latrepirdine and had respiratory arrest from a presumed aspiration event that was assessed as unrelated to the study drug. Overall, 68.5% of those randomized to latrepirdine and 68.0% of those randomized to placebo experienced an adverse event. The most common adverse events in the study were falls, worsening chorea, and somnolence (**Table 4**). Only fatigue and dry mouth occurred more frequently in latrepirdine-treated participants than in placebo-treated participants. Three events indicating suicidality (suicide attempt, parasuicide gesture, and suicidal ideation), all in individuals randomized to placebo, occurred during the study. After baseline, 11 individuals randomized to placebo (5.4%) reported suicidality, and 3 individuals randomized to latrepirdine (1.5%) reported suicidality ($P = .03$) according to the Columbia Classification Algorithm of Suicide

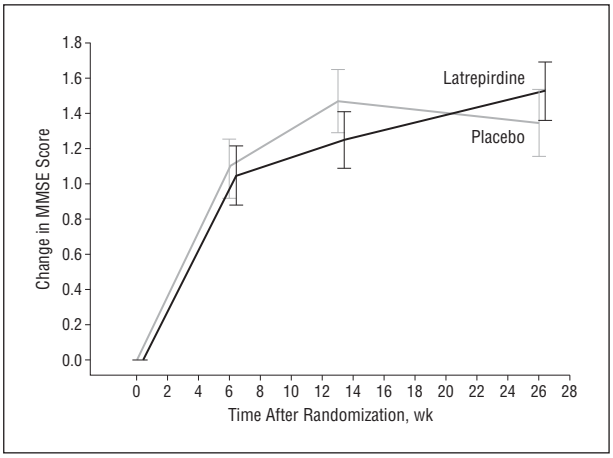

Figure 2. Change over time in the Mini-Mental State Examination (MMSE) score by treatment group. Values plotted are adjusted mean changes from baseline, estimated using a repeated-measures analysis of covariance model with week, region, treatment group, baseline MMSE score, tetrabenazine use, and the interaction between week and treatment group. See the "Statistical Analysis" subsection for details. Bars represent 1 SE of the mean.

Assessment. No significant group differences in vital signs were found except for weight gain in those randomized to latrepirdine (0.97 vs 0.04 kg in those randomized to placebo; treatment effect, 0.94 kg; 95% CI, 0.22-1.65; $P = .01$).

COMMENT

In this study, latrepirdine was not effective in improving cognition or global function in individuals with mild to moderate HD as measured by the MMSE and the CIBIC-Plus. As in previous studies,[4,18,27] latrepirdine was generally well tolerated, but the results did not confirm the potential signal of cognitive improvement on the MMSE observed in the previous HD clinical trial.[8]

Among the potential explanations for the failure to demonstrate benefit in this study include an inadequate dosage of the drug, insufficient duration of treatment, inappropriate outcome measures, or a lack of therapeutic benefit in this population. The dosage of latrepirdine (20 mg 3 times daily) used in this study was the same as in the previous safety and tolerability study,[8] whereas the duration was twice as long. However, no indication of benefit was observed at any time point. Despite the progressive nature of HD, the mean MMSE scores in both groups improved significantly from baseline during the 6-month study, raising questions about the effects of placebo in such trials, although such an effect was not seen in the previous trial.[8] The appropriate cognition and global outcome measures for a cognitive clinical trial in HD are also not established. The MMSE was selected because it is a well-established cognitive outcome measure in cognition trials in Alzheimer disease and Parkinson disease.[28,29] The MMSE has long been used to assess cognitive deficits in HD[17] and demonstrated a potential beneficial signal in the prior study,[8] in contrast to other cognitive outcome measures, including the Alzheimer Disease Assessment Scale–cognitive subscale and cognitive measures of the Unified Huntington's Disease Rating Scale (verbal fluency, symbol digit modalities test, and Stroop color naming, word reading, and interference tests). Other cognitive outcome measures, such as the Montreal Cognitive Assessment[30] or specific measures of executive function or attention, might be more sensitive to changes in HD and await evaluation in future clinical trials. The choice of the CIBIC-Plus as a global outcome measure was more challenging because no sensitive, well-validated instrument for assessing global function in HD during the short term exists, although efforts in developing such an instrument are under way.[31] The study results also advise caution in interpreting efficacy signals in early-stage trials, especially when multiple outcome measures are used without a prespecified hierarchy of analysis or an adjustment for multiple comparisons.

Although the results of this study were disappointing, the trial lays the foundation for future investiga-

Table 3. Distribution of CIBIC-Plus Response (Co-primary Outcome Measure) by Treatment Group[a]

Response	Latrepirdine Group, % (n = 195)	Placebo Group, % (n = 198)
Marked worsening	0.5	1.0
Moderate worsening	5.6	5.6
Minimal worsening	22.6	20.2
No change	40.0	43.9
Minimal improvement	24.1	23.7
Moderate improvement	6.2	4.5
Marked improvement	1.0	1.0

Abbreviation: CIBIC-Plus, Clinician Interview–Based Impression of Change, plus carer interview.
[a] $P = .84$ for comparison of treatment groups (stratified Cochran-Mantel-Haenszel mean score test). See the "Statistical Analysis" subsection for details.

Table 4. Adverse Events by Treatment Group[a]

Event	Latrepirdine Group, No. (%) (n = 200)	Placebo Group, No. (%) (n = 203)
Fall	30 (15.0)	32 (15.8)
Worsening chorea	16 (8.0)	8 (3.9)
Somnolence	11 (5.5)	14 (6.9)
Headache	11 (5.5)	7 (3.4)
Diarrhea	8 (4.0)	9 (4.4)
Nasopharyngitis	9 (4.5)	8 (3.9)
Dysphagia	8 (4.0)	6 (3.0)
Anxiety	8 (4.0)	6 (3.0)
Depression	8 (4.0)	5 (2.5)
Urinary tract infection	5 (2.5)	7 (3.4)
Dry mouth[b]	9 (4.5)	2 (1.0)
Vomiting	4 (2.0)	7 (3.4)
Insomnia	4 (2.0)	7 (3.4)
Nausea	3 (1.5)	7 (3.4)
Fatigue[c]	10 (5.0)	0
Upper respiratory tract infection	4 (2.0)	6 (3.0)
Dizziness	5 (2.5)	5 (2.5)

[a] Adverse events that occurred in at least 10 participants are reported.
[b] $P = .03$, Fisher exact test.
[c] $P < .001$, Fisher exact test.

tions of HD experimental therapeutics aimed at cognition. This study was the largest trial by far of any drug aimed at improving cognition in HD, including 64 centers in 11 countries across 3 continents, with assessments conducted in different languages.[2,32-34] Despite the potential for heterogeneity, the study results were generally consistent across all languages and regions. Enrollment in the study also exceeded expectations, and retention was high, with only 7.4% of participants withdrawing from the 6-month study.

Translating scientific results in HD and other neurodegenerative disorders into efficacious treatments remains a challenge. Advances in our understanding of the origin and cause of HD, the identification of biomarkers for the condition,[35] and the development of therapies aimed at the underlying pathogenesis in HD are progressing.[36] These novel findings, coupled with the infrastructure for clinical investigations, will be needed to assess future treatments aimed at reducing the growing burden of cognitive impairment from HD and related neurodegenerative disorders.[36,37]

Accepted for Publication: June 29, 2012.
Published Online: October 29, 2012. doi:10.1001/2013.jamaneurol.382
Correspondence: E. Ray Dorsey, MD, MBA, 600 N Wolfe St, Meyer 6-181D, Baltimore, MD 21287 (ray.dorsey@jhmi.edu).
Author Contributions: Drs Kieburtz, Landwehrmeyer, and McDermott had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Cudkowicz, Dorsey, Feigin, Hunt, Kayson, Kieburtz, Landwehrmeyer, McDermott, Noonberg, Seitz, Soliveri, and Walker. *Acquisition of data:* Albin, Blindauer, Chiu, Colcher, Corey-Bloom, Craufurd, Cudkowicz, De Michele, de Tommaso, Di Maio, DiPietro, Dorsey, Epping, Feigin, Fischer, Geschwind, Goldstein, Hauser, Hermanowicz, Hjermind, Holt, Ivanco, Jakobsen, Jenkins, Klingelhöfer, Kostyk, Kubu, Leavitt, Loy, Mahant, Marcinkowski, Margolis, McCusker, McDermott, Münchau, Nance, J. E. Nielsen, Niswonger, Noonberg, Novak, Nowak, Orme, Panegyres, Peavy, Priller, Raymond, Reilmann, Rickards, Romrell, Rudzińska, Sacca, Saft, Salvatore, Sass, Seeberger, Seitz, Serpino, Siderowf, Singer, Smith, Squitieri, Storch, Tabrizi, Tempkin, Uhl, Walker, Werner, Wolz, Zielonka, and Zittel. *Analysis and interpretation of data:* Cudkowicz, Dorsey, Feigin, Fisher, Hunt, Kayson, Kieburtz, Landwehrmeyer, McDermott, Nichols, Noonberg, Orme, Seitz, Soliveri, Walker, Watts, Weber, and White. *Drafting of the manuscript:* Dorsey. *Critical revision of the manuscript for important intellectual content:* Albin, Blindauer, Colcher, Corey-Bloom, Craufurd, Cudkowicz, De Michele, de Tommaso, Di Maio, DiPietro, Dorsey, Epping, Feigin, Fischer, Geschwind, Goldstein, Hauser, Hermanowicz, Hjermind, Holt, Ivanco, Jakobsen, Jenkins, Kieburtz, Klingelhöfer, Kostyk, Kubu, Landwehrmeyer, Leavitt, Loy, Mahant, Marcinkowski, Margolis, McCusker, McDermott, Münchau, Nance, Nichols, J. E. Nielsen, Niswonger, Noonberg, Novak, Nowak, Orme, Panegyres, Peavy, Priller, Raymond, Reilmann, Rickards, Romrell, Rudzińska, Sacca, Saft, Salvatore, Sass, Seeberger, Seitz, Serpino, Siderowf, Singer, Smith, Squitieri, Storch, Tabrizi, Tempkin, Uhl, Walker, Werner, Wolz, Zielonka, and Zittel. *Statistical analysis:* McDermott and Watts. *Obtained funding:* Kieburtz. *Administrative, technical, and material support:* Kayson, Kieburtz, Landwehrmeyer, McNees, and Noonberg. *Study supervision:* Cudkowicz, Dorsey, Feigin, Hunt, Kayson, Kieburtz, Landwehrmeyer, McDermott, Noonberg, Seitz, Soliveri, and Walker.
Conflict of Interest Disclosures: Dr Corey-Bloom is a principal investigator on multiple clinical trials for the treatment of cognitive dysfunction and dementia sponsored by pharmaceutical companies such as Elan, Medivation, SIENA, and Teva, in addition to the Huntington Study Group, CHDI Foundation, and Alzheimer's Disease Cooperative Study Group. Dr Hauser has received honoraria or payments for consulting, advisory services, speaking services, or research over the past 12 months for the following: advisory boards (Boehringer Ingelheim Pharmaceuticals, Inc, Teva Neuroscience, Impax Pharmaceuticals, UCB, Inc, GE Healthcare, IPSEN Pharmaceuticals, Novartis, Parkinson Study Group, Solvay, Quintiles, and Biogen Idec), speakers' bureau (Allergan Neuroscience, GlaxoSmithKline, Teva Neuroscience, Boehringer Ingelheim Pharmaceuticals, Inc, Novartis Pharmaceuticals, and IPSEN Pharmaceuticals), consulting (Bial, Lundbeck, Biogen Idec, Boehringer Ingelheim, Chelsea Therapeutics, GE Healthcare, Impax, Santhera Pharmaceuticals, Merck Serono/EMD Serono, Solvay Pharmaceuticals, Synosis Therapeutics, Schering-Plough, Shire Pharmaceuticals, Inc, XenoPort, Inc, Medivation, Addex, Adamas Pharmaceuticals, and Noven Pharmaceuticals), research (PICO-Tesla, Schwartz Pharma, Genzyme, Acadia, Solvay Pharmaceuticals, Impax, Teva Neuroscience, [Merck] Serono, Schering-Plough, Novartis Pharmaceuticals, IPSEN Pharmaceuticals, XenoPort Pharmaceuticals, Chelsea Therapeutics, Allergan Neuroscience, Molecular Biometrics, The Michael J. Fox Foundation for Parkinson's Research, and the National Parkinson Foundation), and royalties (University of South Florida). In addition, Dr Hauser has consulted in litigation with lawyers representing various current and former manufacturers of welding consumables. Dr Hermanowicz reports research, clinical trial, speaking honoraria, and salary support from the California Institute for Regenerative Medicine, Huntington Study Group, Lundbeck, and University of California, Irvine. Dr Kieburtz reports serving as a consultant to the National Institutes of Health (National Institute of Neurological Disorders and Stroke), US Food and Drug Administration, US Veterans Administration, Abbott, Acorda, Aptiv, Biogen Idec, Biotie, Biovail, Boehringer Ingelheim, Ceregene, Civitas, Clintrex, Cynapsus, EMD Merck Serono, Genzyme, Impax, Intec, Ipsen, Isis, Knopp, Eli Lilly, Link Medicine, Lundbeck, LZ Therapeutics, Merz, Novartis, Orion, Otsuka, Pharm2B, Phytopharm, Schering-Plough, Siena Biotech, Synosia, Solvay, Synagile, Teva, UCB Pharma, Vaccinex, Vectura, and XenoPort; he also reports grants and research support from Medivation, The Michael J. Fox Foundation, the National Institutes of Health (National Eye Institute, National Institute of Neurological Disorders and Stroke, National Institute on Aging, and

the Eunice Kennedy Shriver National Institute of Child Health and Human Development), NeuroSearch, and Pfizer, as well as legal consulting for Pfizer, Thompson Hine, and welding rod litigation defendants. Dr Landwehrmeyer reports receiving consultancy fees from Siena Biotech, AOP Orphan, Teva, and GlaxoSmithKline, as well as grants for Huntington disease–related studies for the Institution University of Ulm from the European Commission, CHDI Foundation, Medivation, NeuroSearch, Novartis, Medesia, and Amarin. Dr McNees has served as a clinical project manager for Medivation from 2007 to the present. Dr Margolis disclosed funding for this project from Medivation and Pfizer. Dr Noonberg works for Medivation and holds stock in the company. Dr Saft has received honoraria from Temmler Pharma Gmbh & Co KG and payment from the European Huntington's Disease Network for the REGISTRY study, from Novartis Pharmaceuticals Switzerland for the AFQ056 study, from NeuroSearch for the ACR16 Study, and from Siena Biotech for Selisistat studies, as well as research support from Teva Pharma GmbH; no financial interests are related to the material in the manuscript. None of the HORIZON investigators of the Huntington Study Group or the European Huntington's Disease Network has had equity interest or received any personal remuneration from the sponsoring companies since the initiation of the study. All authors completed and submitted the International Committee of Medical Journal Editors form for financial disclosure.

Funding/Support: The study was funded by a grant from Medivation to the University of Rochester and in turn through subcontracts to the participating research sites. The study was also sponsored by Pfizer.

Role of the Sponsors: The sponsors contributed to the design and conduct of the study, interpretation of the data, and review of the article as coauthors of the manuscript.

Group Information: The HORIZON Investigators of the Huntington Study Group and European Huntington's Disease Network are as follows: *Steering Committee:* Karl Kieburtz (principal investigator),* Georg B. Landwehrmeyer (coprincipal investigator),* Merit Cudkowicz,* E. Ray Dorsey,* Andrew Feigin,* Victoria Hunt,* Elise Kayson,* Michael McDermott,* Sarah Noonberg,* Wendy Seitz,* Paola Soliveri,* Francis Walker.* *Participating Sites (investigators and coordinators): Bern, Switzerland:* Jean-Marc Burgunder, Irene Romero, Anouk Magara, Yanik Stebler. *Birmingham and Solihull Mental Health Foundation, Birmingham and Solihull, England:* Hugh Rickards,* Jan Wright, Jenny De Souza. *Cambridge Centre for Brain Repair, Cambridge, England:* Roger A. Barker, Sarah Mason, Anna Di Pietro,* Anna Goodman, Deidre O'Keeffe. *Centre Hospitalier Affilie Universitaire de Québec-Hôpital de l'Enfant-Jésus, Québec City, Québec, Canada:* Melanie Langlois, Germain Ferland, Louis Verret. *CHUM–Hospital Notre-Dame, Montreal, Québec, Canada:* Sylvain Chouinard, Suzanne Paris, Christiane LePage. *Churchill Hospital, Oxford University Hospitals NHS Trust, Oxford, England:* Andrea H. Nemeth, Claire Merritt, Caroline Cox, Therese Astbury, Sarah Murphy. *Cleveland Clinic, Cleveland, Ohio:* Anwar Ahmed, Patricia St Marie, Rose Anne Berila, Cynthia Kubu.* *Colorado Neurological Institute, Englewood:* Vicki Segro, Rajeev Kumar, Diane Erickson, Jay Schneiders. *Columbia University Medical Center, New York, New York:* Steven Frucht, Paula Wasserman, Carol Moskowitz. *Duke University, Durham, North Carolina:* Burton Scott, Peggy Perry-Trice, Sarah Wyne. *Fondazione IRCCS Istituto Neurologico C. Besta, Milano, Italy:* Paola Soliveri, Dominga Parida, Veronica Redaelli. *Gabinet Zabiegowy in Gdansk, Gdansk, Poland:* Witold Soltan, Piotr Robowski, Malgorzata Nowak,* Michal Schinwelski, Artur Dziadkiewicz. *Guy's Hospital, London, England:* Thomasin Andrews, Deborah Ruddy, Andrew Dougherty. *Hamburg University Hospital, Hamburg, Germany:* Kai Boelmans, Jenny Schmalfeld, Alexander Münchau,* Simone Zittel.* *Hereditary Neurological Disease Centre, Wichita, Kansas:* William Mallonee, Greg Suter, Jeremy Tan. *Idaho Elks Rehabilitation Center, Boise:* Lauren Seeberger,* Jane Harris, Jamie Champion. *Indiana University School of Medicine, Indianopolis:* Joanne Wojcieszek, Joann Belden, Katie Price, Marsha Hughes-Gay, Gwen Sprehn. *IRCCS Neuromed–Unita di Neurogenetica, Pozzilli, Italy:* Ferdinando Squitieri,* Tiziana Martino, Francesca De Gregorio, Annunziata De Nicola, Francesca Elifani. *Johns Hopkins University, Baltimore, Maryland:* Adam Rosenblatt, Nadine Yoritomo, Russell Margolis,* Paige Nichols.* *Karolinska Hospital, Stockholm, Sweden:* Sven E. Palhagen, Arja Vehkala Hoglund, Martin Paucar, Tina Wallden Reza-Soltani. *Klinik Taufkirchin, München, Germany:* Antonie Beister, Tina Raab, Janina Kieni, Caroline Schrenk. *Krakow Institution, Krakow, Poland:* Krzysztof Banaszkiewicz, Jakub Misztela, Magdalena Wojcik, Elzbieta Szczygiel, Marta Golosz, Monika Rudzińska.* *Leiden University Medical Centre, Leiden, the Netherlands:* Raymund A. C. Roos, Simon J. A. van den Bogaard, Reineke Bos, Suzanne J. Booij. *London Health Sciences Centre, London, England:* Christopher Hyson, Julie Megens, Emilija Makaji, Mary Jenkins.* *Massachusetts General Hospital, Boston:* Steven Hersch, Susan Maya, Caleb Dresser, Diana Rosas. *Medical College of Wisconsin, Milwaukee:* Karen Blindauer,* Clara Schindler, Serena Hung. *Medivation, San Francisco, California:* Alexander Aaron McNees.* *National Hospital for Neurology and Neurosurgery, London, England:* Sarah Tabrizi,* Marianne Novak,* Miranda Say, Aakta Patel. *Neurodegenerative Disorders Research, Subiaco, Australia:* Peter Panegyres,* Nicola Lewis, Samantha Jukich, Catherine Faull. *Neurogenetics Clinic, Copenhagen, Denmark:* Lena Elisabeth Hjermind,* Oda Jakobsen,* Asmus Vogel, T. Rune Nielsen, Jørgen E. Nielsen.* *Ohio State University, Columbus:* Sandra Kostyk,* Allison Seward, Punit Agrawal. *Oregon Health & Science University, Portland:* Jeff Kraakevik, Penelope Hogarth, April Wilson, Joyce Lear. *Rigshospitalet, Copenhagen University Hospital, Memory Disorders Research Unit, Ruhruniversitat Bochum, Copenhagen, Denmark:* Peter H. Kraus, Carsten Saft,* Tanja Steiner, Rainer Hoffmann, Christiane Stamm, Joanna Schollhammer, Idun Uhl,* Barbara Kaminski. *Sheffield Children's Hospital, Sheffield, England:* Kirsty O'Donovan, Oliver Quarrell, Louise Nevitt. *Southampton General Hospital, Hampshire, England:* Christopher Kipps, Angela Hare, Kerry Gunner, Elaine Hayward. *Struthers Parkinson's Center, Golden Valley, Minnesota:* Martha Nance,* Judy Hamerlinck, Catherine Wielinski. *St Vincent's Aged Psychiatry Service, Melbourne, Australia:* Olga Yastrubetskaya, Edmond Chiu,*

Phyllis Chua, Bernadette Mannaa. *Università di Bari, Bari, Italy:* Marina de Tommaso,* Claudia Serpino,* Claudia Cormio, Vittorio Sciruicchio. *Università Federico II, Naples, Italy:* Giuseppe De Michele,* Luigi Di Maio,* Cinzia Valeria Russo, Francesco Sacca,* Elena Salvatore,* Tecla Tucci. *Universitätsklinikum Carl Gustav Carus, Dresden, Germany:* Martin Wolz,* Lisa Klingelhöfer,* Annett Wolz, Simone Schmidt, Alexander Storch.* *Universitätsklinikum Charité, Berlin, Germany:* Eike Spruth, Silvia Thiel, Britta Neumann, Harald Gelderblom, Josef Priller.* *University of Aachen, Aachen, Germany*: Christian Sass,* Daniela Probst, Cornelius Werner.* *University of British Columbia, Vancouver, British Columbia, Canada:* Blair R. Leavitt,* Allison Coleman, Lynn Raymond.* *University of California, Davis Medical Center:* Vicki Wheelock, Teresa Tempkin,* Kathleen Baynes. *University of California, Irvine:* Neal Hermanowicz,* Shari Niswonger,* Maureen Haske-Palomino. *University of California, Los Angeles:* Yvette Bordelon, Angelina Gratiano, Arik Johnson. *University of California, San Diego:* Jody Corey-Bloom,* Jody Goldstein,* Guerry Peavy.* *University of California, San Francisco:* Michael Geschwind,* Jonathan Gooblar, Cindy Barton. *University of Florida, Gainesville:* Hubert Fernandez, Ramon Rodriguez, Michele Suelter, Marie Daniels, Janet Romrell,* Camille Swartz. *University of Iowa, Iowa City:* Leigh Beglinger, Eric Epping,* Elijah Waterman, Megan M. Smith.* *University of Kansas Medical Center, Lawrence:* Richard Dubinsky, Hilary Dubinsky, Carolyn Gray. *University of Manchester, Manchester Academic Health Sciences Centre, and Central Manchester University Hospitals NHS Foundation Trust, Manchester, England:* David Craufurd,* Elizabeth Howard, Mary Jones, Helen Murphy. *University of Maryland School of Medicine, Baltimore:* Karen Anderson, Constance Nickerson, Jennifer De Santo, Tamara Rigaud, Nancy Zappala, Bradley Robottom. *University of Miami, Miami, Florida:* Carlos Singer,* Monica Quesada, Kenia Rodriguez-Spengler, Rene Hernandez Cardenache. *University of Muenster, Muenster, Germany:* Ralf Reilmann,* Stefan Bohlen, Eva-Maria Hoelzner. *University of Pennsylvania, Philadelphia:* Amy Colcher,* Heather Maccarone, Lisa Altin, Andrew Siderowf.* *University of Pittsburgh, Pittsburgh, Pennsylvania:* Timothy John Greenamyre, Nancy Lucarelli, Larry Ivanco.* *University of Rochester, Rochester, New York:* Frederick Marshall, Charlyne Hickey, Lisa Deuel, Kevin Biglan. *University of Ulm, Ulm, Germany:* Sigurd D. Sussmuth, Michael Orth, Sonja Trautmann, Carolin Eschenbach. *University of Washington, Seattle:* Ali Samii, Alma Macaraeg. *USI-MED Poznan, Poznan, Poland:* Daniel Zielonka,* Anna Ciesielska, Jerzy T. Marcinkowski,* Justyna Sempolowicz, Hanna Karaskiewicz. *Wake Forest University, Winston-Salem, North Carolina:* Francis Walker, Christine O'Neill, Ihtsham Haq. *Warsaw–IPIN Institute of Psychiatry and Neurology, Warsaw, Poland:* Grezegorz Witkowski, Jakub Antczak, Rafal Rola, Przemyslaw Richter, Maria Rakowicz, Katarzyna Jachinska. *Washington University, St Louis, Missouri:* Susan Criswell, Patricia Deppen, Kathleen Wharton. *Westmead Hospital, Sydney, Australia:* Neil Mahant,* Elizabeth McCusker,* Jane Griffith, Clement Loy,* Linda Stewart. *Biostatistics and Coordination Center:* Danielle Fisher,* Dustina Holt,* Constance Orme,* Arthur Watts,* Joseph Weber,* Kathy White.* *Safety Monitoring Committee:* Robert A. Hauser,* Roger Albin,* Christopher Coffey, Wilhelm Fischer,* Janis Miyasaki.

Additional Contributions: Alexandra Gangler, BA, assisted with the preparation of the manuscript. Michael P. McDermott, PhD, and Arthur Watts, BS, conducted the biostatistical analyses for the study. The Huntington Study Group Coordination and Biostatistics Center at the University of Rochester independently compiled and analyzed the data for this study.

REFERENCES

1. Walker FO. Huntington's disease. *Lancet*. 2007;369(9557):218-228.
2. Beglinger LJ, Adams WH, Paulson H, et al. Randomized controlled trial of atomoxetine for cognitive dysfunction in early Huntington disease. *J Clin Psychopharmacol*. 2009;29(5):484-487.
3. Bachurin SO, Shevtsova EP, Kireeva EG, Oxenkrug GF, Sablin SO. Mitochondria as a target for neurotoxins and neuroprotective agents. *Ann N Y Acad Sci*. 2003; 993:334-349.
4. Sabbagh MN, Shill HA. Latrepirdine, a potential novel treatment for Alzheimer's disease and Huntington's chorea. *Curr Opin Investig Drugs*. 2010;11(1):80-91.
5. Bezprozvanny I. The rise and fall of Dimebon. *Drug News Perspect*. 2010;23(8): 518-523.
6. Kim J, Moody JP, Edgerly CK, et al. Mitochondrial loss, dysfunction and altered dynamics in Huntington's disease. *Hum Mol Genet*. 2010;19(20):3919-3935.
7. Mochel F, Haller RG. Energy deficit in Huntington disease: why it matters. *J Clin Invest*. 2011;121(2):493-499.
8. Kieburtz K, McDermott MP, Voss TS, et al; Huntington Disease Study Group DIMOND Investigators. A randomized, placebo-controlled trial of latrepirdine in Huntington disease [published correction appears in *Arch Neurol*. 2010;67(4):492]. *Arch Neurol*. 2010;67(2):154-160.
9. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. *Mov Disord*. 1996;11(2):136-142.
10. Shoulson IKR, Rubin A, Goldblatt D, et al. Assessment of functional capacity in neurodegenerative movement disorders: Huntington's disease as a prototype. In: Munsat TL, ed. *Quantification of Neurological Deficit*. Boston, MA: Butterworth; 1989:271-283.
11. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12(3):189-198.
12. Tombaugh TN, McIntyre NJ. The Mini-Mental State Examination: a comprehensive review. *J Am Geriatr Soc*. 1992;40(9):922-935.
13. Joffres C, Graham J, Rockwood K. Qualitative analysis of the Clinician Interview-Based Impression of Change (Plus): methodological issues and implications for clinical research. *Int Psychogeriatr*. 2000;12(3):403-413.
14. Litvinenko IV, Odinak MM, Mogil'naya VI, Emelin AY. Efficacy and safety of galantamine (reminyl) for dementia in patients with Parkinson's disease (an open controlled trial). *Neurosci Behav Physiol*. 2008;38(9):937-945.
15. Minett TS, Thomas A, Wilkinson LM, et al. What happens when donepezil is suddenly withdrawn? an open label trial in dementia with Lewy bodies and Parkinson's disease with dementia. *Int J Geriatr Psychiatry*. 2003;18(11):988-993.
16. Orgogozo JM, Rigaud AS, Stöffler A, Möbius HJ, Forette F. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). *Stroke*. 2002;33(7):1834-1839.
17. Folstein SE. *Huntington's Disease: A Disorder of Families*. Baltimore, MD: Johns Hopkins University Press; 1989.
18. Doody RS, Gavrilova SI, Sano M, et al; Dimebon Investigators. Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. *Lancet*. 2008;372(9634):207-215.
19. Hoth KF, Paulsen JS, Moser DJ, Tranel D, Clark LA, Bechara A. Patients with Huntington's disease have impaired awareness of cognitive, emotional, and functional abilities. *J Clin Exp Neuropsychol*. 2007;29(4):365-376.
20. Paulsen JS, Ready RE, Hamilton JM, Mega MS, Cummings JL. Neuropsychiatric aspects of Huntington's disease. *J Neurol Neurosurg Psychiatry*. 2001; 71(3):310-314.
21. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308-2314.
22. Galasko D, Bennett D, Sano M, et al; The Alzheimer's Disease Cooperative Study.

An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. *Alzheimer Dis Assoc Disord*. 1997;11(suppl 2):S33-S39.
23. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007;164(7):1035-1043.
24. Molenberghs G, Thijs H, Jansen I, et al. Analyzing incomplete longitudinal clinical trial data. *Biostatistics*. 2004;5(3):445-464.
25. Little RJA, Rubin DB. *Statistical Analysis With Missing Data*. 2nd ed. Hoboken, NJ: Wiley & Sons; 2002.
26. Landis JR, Cooper MM, Kennedy T, Koch GG. A computer program for testing average partial association in three-way contingency tables (PARCAT). *Comput Programs Biomed*. 1979;9(3):223-246.
27. Bachurin S, Bukatina E, Lermontova N, et al. Antihistamine agent Dimebon as a novel neuroprotector and a cognition enhancer. *Ann N Y Acad Sci*. 2001;939: 425-435.
28. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med*. 2004;351(24):2509-2518.
29. Ravina B, Putt M, Siderowf A, et al. Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study. *J Neurol Neurosurg Psychiatry*. 2005;76(7):934-939.
30. Videnovic A, Bernard B, Fan W, Jaglin J, Leurgans S, Shannon KM. The Montreal Cognitive Assessment as a screening tool for cognitive dysfunction in Huntington's disease. *Mov Disord*. 2010;25(3):401-404.
31. Tabrizi SJ, Scahill RI, Durr A, et al; TRACK-HD Investigators. Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurol*. 2011;10(1):31-42.
32. Cubo E, Shannon KM, Tracy D, et al. Effect of donepezil on motor and cognitive function in Huntington disease. *Neurology*. 2006;67(7):1268-1271.
33. de Tommaso M, Specchio N, Sciruicchio V, Difruscolo O, Specchio LM. Effects of rivastigmine on motor and cognitive impairment in Huntington's disease. *Mov Disord*. 2004;19(12):1516-1518.
34. Ondo WG, Mejia NI, Hunter CB. A pilot study of the clinical efficacy and safety of memantine for Huntington's disease. *Parkinsonism Relat Disord*. 2007;13(7): 453-454.
35. Weir DW, Sturrock A, Leavitt BR. Development of biomarkers for Huntington's disease. *Lancet Neurol*. 2011;10(6):573-590.
36. Klein C, Krainc D, Schlossmacher MG, Lang AE. Translational research in neurology and neuroscience 2011: movement disorders. *Arch Neurol*. 2011;68 (6):709-716.
37. Risks GH. *Mortality and Burden of Diseases Attributable to Selected Major Risks*. Geneva, Switzerland: World Health Organization; 2009.