A Controlled Clinical Trial of Baclofen As Protective Therapy in Early Huntington's Disease

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We carried out a controlled clinical trial to examine the potential of baclofen to slow the functional decline of patients with early Huntington's disease (HD). The basis of the trial was: (1) the hypothesis that excitatory amino acid neurotransmission mediates the neuronal degeneration of HD, (2) preclinical evidence that baclofen retards corticostriatal release of glutamate and aspartate, and (3) reports that baclofen produces short-term clinical benefits in some HD patients. Sixty patients with early HD were randomized to chronic baclofen, 60 mg/day, or placebo treatments and followed systematically for up to 42 months. Total functional capacity was not favorably influenced by baclofen treatment. Factors that contributed, although nonsignificantly, to a more rapid rate of total functional capacity decline included younger age (< 35 years), earlier stage (stage I) of illness, paternal inheritance of the HD gene, and baclofen treatment. Our patients declined at a pace slower than that observed in other prospective studies, a finding likely due to selection criteria, avoidance of neuroleptic therapy, and strong psychosocial support.

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Huntington's disease (HD) is a dominantly inherited neurodegenerative disease linked to gene expression on the short arm of chromosome 4 and characterized clinically by disordered movement, intellectual decline, and psychiatric illness [1, 2]. Clinical features surface gradually in HD gene carriers and progress inexorably to serious disability and early death, reflecting selective and progressive neuronal degeneration and a resulting pattern of neurochemical pathology [3, 4]. Pharmacological strategies aimed at rectifying neurochemical pathology have been unsuccessful, largely because of the multiplicity of neurochemical changes and the progressive nature of underlying neuronal degeneration [5].

Recent positron emission tomography studies examining early HD patients and persons at risk for developing HD have demonstrated reduced fluorodeoxyglucose metabolism in the striatum shortly before or coincidental with the onset of early clinical features [6–8]. These observations suggest that striatal metabolic perturbations just precede or coincide with the earliest stages of illness and support experimental strategies aimed at slowing the progression of early HD. Basic and clinical studies implicate excitatory amino acid neurotransmission, particularly that involving glutamate and the N-methyl-D-aspartate (NMDA) receptor, in the pathogenesis of HD [9, 10]. Attenuation of corticostriatal excitatory neurotransmission might therefore be expected to slow neuronal death and the pace of the progression of the illness [10, 11].

Based on the foregoing observations and hypothesis, we began a controlled clinical trial in 1982 to evaluate the potential protective effects of baclofen [β-(*p*-chlorophenyl)-γ-aminobutyric acid] in slowing the progression of early HD [11]. Preclinical studies indicated that baclofen inhibits corticostriatal release of glutamate and aspartate at clinically relevant dosage [12–14] and exerts some protective effect against potent neurotoxins such as kainic acid in animal models of HD [15–17]. Several clinical studies also suggested that baclofen, a putative agonist at one of the receptor sites for γ-aminobutyric acid ($GABA_B$), [18, 19], may reduce choreic movements and improve functional capacity in some HD patients [20–22].

The primary objective of our placebo-controlled, double-blind study was to determine whether long-

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term therapy with baclofen, 60 mg/day, would decrease the rate of functional decline in patients with early HD during 30 months or more of prospective evaluation.

Methods

Patients were eligible for the trial if (1) they were 18 years old or older; (2) their HD diagnosis was determined by presence of an unexplained movement disorder and a confirmatory family history of HD; (3) they were in the early stages (stages I and II) of illness as determined by a mean total functional capacity (mTFC) score [23–25], computed by averaging the scores assessed by seven blinded raters, obtained while patients were drug-free for at least 4 weeks; (4) they were in satisfactory general medical health; and (5) a family member or close friend (chaperon) was willing to support and accompany the patient through long-term evaluations. Patients with serious psychiatric illness (major depression requiring antidepressant medication, psychotic illness requiring antipsychotics, actively suicidal behavior) were excluded from participation. Informed consent was obtained from all eligible patients and their chaperons.

Following baseline evaluation, subjects were randomized to active baclofen or matching placebo treatments with assignments balanced for age at entry (< 35 years old versus $\geq$ 35 years old) and stage of illness (stage I: mTFC = 11–13 units; stage II: mTFC = 7–10 units). For subjects assigned to active baclofen, dosage of the racemic preparation (Lioresal 10-mg tablet) was started at 10 mg/day and increased by 10 mg/day until a dosage of 60 mg/day (20 mg at 8 AM, 2 PM, and 8 PM) was attained. Subjects assigned to placebo received matching tablets of inert composition.

Subjects were enrolled in this study from 1982 to 1985 and followed longitudinally until its conclusion in 1987. They were observed in our clinical research center during the first week of dosage adjustment and reevaluated thereafter at approximately 6 months, 18 months, 30 months, and 42 months. Subjects remaining in the study at conclusion were instructed to discontinue their experimental medications over 1 week and to complete a self-rating scale just prior to discontinuation of medication and at 4 weekly intervals thereafter. The rating scale ranged continuously from 0 (feeling very poorly) to 10 (feeling exceptionally well). Subjects were not permitted any psychoactive medication throughout the trial unless judged by the principal investigator to have developed seriously disabling movements, depression, or psychosis. If one or more of these problems developed, open trials were initiated using tetrabenazine for disabling hyperkinetic movement disorder, desipramine for depression, and haloperidol for psychosis.

The primary response variable was the change in TFC scores [23–25] between baseline and follow-up evaluations at 30 months. TFC was determined independently by seven clinical investigators (two neurologists, two nurses, one psychiatrist, one psychologist, one speech therapist) at baseline and at all follow-up evaluations using a scale ranging from 13 (full capacity or normal) to 0 (total incapacity) units [24, 25]. This rating scale has demonstrated validity with respect to clinical [25–28] and radiographic [6, 25, 29, 30] correlates of HD and high interobserver [25, 31] and cross-cultural [32, 33] reliability. A variety of clinical, radiographic, and neurochemical cerebrospinal fluid indexes were obtained prospectively as secondary response variables to explore correlates of TFC decline in early HD. These findings will be reported separately.

Sample size requirements were estimated from our preliminary data indicating an average decline in TFC of 1.25 units/year in HD patients representing all stages of illness [24, 25]. The dropout rate was estimated at 10% of the subjects by 30 months of follow-up. The significance level was set at 5% ($\alpha = 0.05$) for a one-sided, two-sample Student's t test for detecting any therapeutic effect. Power was computed assuming standard deviations of the change in TFC over 30 months of 1.0, 1.5, and 2.0 units. For a total sample size of 60 subjects (30 on placebo and 30 on baclofen) completing 30 months of evaluation, the estimated power of the trial for detecting a minor therapeutic effect (20% reduction in TFC decline) was approximately 0.75, 0.48, and 0.33 for standard deviations of, respectively, 1.0, 1.5, and 2.0. Power of the trial for detecting a major therapeutic effect (40% reduction in TFC decline) was approximately 0.99, 0.93, and 0.76 for the above standard deviations, respectively [34]. Sample size estimates and power were reassessed (post-hoc analysis) after completion of the primary analyses.

The trial was monitored every 6 months by an independent committee that assessed potential adverse effects and efficacy of experimental treatments. A policy for recommending premature termination of the trial was established to detect any significant adverse differences (nominally $p < 0.05$) and more striking differences in efficacy (nominally $p < 0.01$). Premature termination was not recommended, and final data analysis of treatment effects began in 1987 when the last entered subject completed 30 months of evaluation.

How well the study was blinded was assessed just prior to washout of experimental drugs by administering a modified questionnaire [35] probing for a best guess as to whether the subject was receiving placebo or active baclofen treatments. Each subject and chaperon was asked to respond, and raters responded for all subjects. Blindness was analyzed by the chi-square statistic to assess whether guesses as to treatment showed significant agreement with actual treatment assignment. Washout effects of discontinuing baclofen were analyzed by Student's t tests comparing subject's self-rating scores over the 4-week period of assessment with respect to baclofen and placebo treatments.

Medication compliance was monitored by reports from subject diaries and counts of unused tablets returned to our pharmacy at follow-up evaluations. Diet was restricted only to the extent that subjects were advised to avoid food supplemented with monosodium glutamate. High levels of activity were encouraged.

Analyses of the primary response variable were carried out by an unbalanced three-way analysis of variance comparing the change in TFC between baseline and follow-up visits in placebo- and baclofen-treated groups [36]. The primary model assumed no interaction between age at entry, stage of illness, and treatments, but models including interaction effects [37] were also fitted. The primary analysis was carried out considering each investigator an independent rater, because evaluations were conducted independently and from different clinical perspectives. An analysis combining the scores obtained by seven raters into mTFC scores was carried out later to help condense the findings. In view of our

Table 1. Distribution of Continuing Subjects at Baseline and Follow-up Evaluations

Group	Baseline[a]	6 Months	18 Months	30 Months	42 Months
Placebo group	30	29	27	26	14
Baclofen group	30	27	24	23	15
Total	60	56	51	49[b]	29[c]

[a] At baseline, those assigned to placebo included 16 subjects in stage I and 14 in Stage II, and 9 subjects less than 35 years old and 21 subjects 35 years old or older; those assigned to baclofen included 18 subjects in stage I and 12 in stage II and 8 subjects less than 35 years old and 22 subjects 35 years old or older.
[b] Reflects 11 dropouts at 30 months.
[c] Represents continuing subjects at 42 months who entered study within initial years of staggered entry.

Table 2. Demographic Profile at Entry of Cohort (n = 49) Completing 30 Months of Evaluation[a]

Group	N	Age (yr)[b]	Sex	Age at Onset of Symptoms (yr)[b]	Duration of Illness from Onset of Symptoms (yr)	Age at Diagnosis (yr)[b]	Duration of Illness from Diagnosis (yr)	Inheritance of the HD Gene[c]
Placebo group	26	40.8 ± 10.6	13M, 13F	35.4 ± 11.1	5.4 ± 2.8	38.7 ± 11.0	2.0 ± 2.5	13P, 13M
Baclofen group	23	38.0 ± 10.2	11M, 12F	32.8 ± 10.9	5.2 ± 3.7	36.4 ± 10.3	1.7 ± 2.0	15P, 8M
Total	49	39.5 ± 10.4	24M, 25F	34.2 ± 10.9	5.3 ± 3.3	37.6 ± 10.7	1.9 ± 2.3	28P, 21M

[a] Values are expressed as the mean ± standard deviation.
[b] No significant differences were found between placebo and baclofen groups with respect to the following by Wilcoxon rank sums: age: $z = 0.762$, $p = 0.446$; age at onset: $z = 0.632$, $p = 0.528$; age at diagnosis: $z = 0.471$, $p = 0.638$.
[c] Mode of inheritance: $\chi^2 = 2.443$, $p = 0.118$.

P = paternal descent; M = maternal descent; HD = Huntington's disease.

post-hoc analysis, all significance values were reported for a two-sided test.

Results

Entry and Follow-up of Patients

Sixty HD patients were enrolled in the trial, 21 in the first year (1982–1983), 25 in the second year (1983–1984), and 14 in the third year (1984–1985).

Table 1 summarizes the distribution of continuing subjects at baseline and follow-up evaluations. By conclusion of the study in 1987, 49 subjects had completed 30 months of evaluation, while 11 subjects (18%) had terminated participation prior to 30 months. Twenty-nine subjects who had completed 30 months of evaluation by 1986 consented to continue experimental drugs to 42 months of follow-up. This extended evaluation of 29 subjects took place while the last group of enrolled subjects (n = 14) was completing 30 months of follow-up.

The demographic profile of the cohort (n = 49) completing 30 months of evaluation is summarized in Table 2. Subject groups for placebo and baclofen treatments were comparable at entry with respect to age, sex, and duration of illness. Subjects with paternal inheritance of the HD gene were assigned randomly but disproportionately to the baclofen group (20/30 = 66.7%) compared with the placebo group (14/30 = 46.7%), but this difference was not significant by chi-square analysis ($\chi^2 = 2.443$, $p = 0.118$) or Fisher's exact test ($p = 0.192$ for two-tailed test). Eleven subjects dropped out of the trial before 30 months of follow-up (see Table 1), including 4 after baseline, 5 after 6 months, and 2 after 18 months. Overall, 7 subjects assigned to baclofen dropped out of the study after 9.3 ± 6.3 (mean ± SD) months of evaluation, and 4 assigned to placebo dropped out after 12.3 ± 9.2 months. Premature terminations in the baclofen group included 2 subjects who developed increased involuntary movements (1 within 3 weeks and 1 within 6 months of initiating treatment), 1 subject who became increasingly psychotic, and 1 subject who remained depressed despite a trial of desipramine. Personal and logistical problems were the main reasons for dropout in 3 baclofen- and 4 placebo-treated subjects.

Six subjects (3 on placebo and 3 on baclofen) developed depression sufficiently disabling to warrant antidepressant pharmacotherapy. Four of these subjects (2 on placebo and 2 on baclofen) had histories of depression. Two subjects on baclofen developed psychotic features with persecutory delusions, prompting discontinuation of experimental drug and institution of antipsychotic therapy. Baclofen was restarted in 1 of these subjects who also required maintenance haloperidol 1 mg/day; the other subject was withdrawn from the study. No subject developed disabling movement disorder requiring symptomatic therapy, but 3 subjects on baclofen reported increased and bothersome involuntary movements, requiring discontinuation of experimental treatments at 1 month, 8 months, and 30 months after entry. Compliance in taking experimental

Table 3. Estimate and Standard Error for Age, Stage, and Treatment Effects Measuring Change in TFC for Each Rater and for mTFC Between Baseline and 30-Month Evaluations (n = 49)[a]

Rater No.	Reference Values for Age < 35, Stage I, Placebo	Age ≥ 35 vs Age < 35	Stage II vs Stage I	Baclofen vs Placebo
1	−1.51 (0.48)	+0.67 (0.46)	−0.06 (0.44)	−0.43 (0.44)
2	−1.94 (0.53)	−0.27 (0.51)	−0.36 (0.49)	−0.60 (0.49)
3	−1.95 (0.65)	+0.48 (0.59)	+0.55 (0.57)	−0.43 (0.57)
4	−1.87 (0.71)	+0.45 (0.68)	+1.34 (0.66) (p = 0.048)	−1.40 (0.65) (p = 0.037)
5	−1.30 (0.58)	+0.55 (0.55)	+0.45 (0.54)	−0.24 (0.53)
6	−1.81 (0.61)	+0.13 (0.58)	+0.74 (0.57)	−1.07 (0.56)
7	−2.62 (0.66)	+0.42 (0.63)	+1.49 (0.61) (p = 0.019)	−0.64 (0.60)
mTFC without inheritance	−1.87 (0.44)	+0.35 (0.42)	+0.60 (0.41)	−0.68 (0.40)
mTFC with inheritance	−1.54 (0.50)	+0.31 (0.42)	+0.55 (0.41)	−0.61 (0.40)

[a] A negative (−) estimate indicates a relatively deleterious effect on TFC, while a positive (+) estimate indicates a relatively beneficial effect on TFC. Variables are analyzed by three-way analysis of variance comparing the listed parameter with its standard error. A t statistic is derived by dividing estimate by the standard error.

TFC = total functional capacity; mTFC = mean TFC.

medications averaged 94% of total doses by subject reports and 91% of total doses by pill counting.

Treatment Effects

Table 3 displays estimates and standard errors of the treatment effect and stratifying variables for seven blinded raters by three-way analysis of variance for change in TFC with respect to age, stage, and treatment (i.e., in symbolic notation [37] change in TFC over 30 months = age + stage + treatment). An additive model with no interactions was assumed. Reference values in this analysis [37] were set for age less than 35 years, stage I, and placebo-treated subjects. All raters indicated a significant decline over 30 months for this reference group. Analyzing the independent influence of treatment, one rater (Rater 4) judged baclofen to be significantly (p = 0.037) detrimental compared to placebo for change in TFC at 30 months. The other raters rated baclofen as contributing to a slightly greater decline in TFC compared with placebo, but none of these treatment effects were significant. Regardless of treatment, two raters (Raters 4 and 7 in Table 3) judged the decline in TFC at 30 months to be significantly more rapid for stage I than for stage II subjects. Six of the seven raters judged TFC decline as more rapid in younger (< 35 years) subjects but these differences were not significant.

TFC data were condensed to a mean value of the values obtained by the seven raters (MTFC) to summarize overall magnitude of treatment effects (Table 3). This analysis took into account the influences of age, stage, treatment, and mode of HD gene inheritance. In comparison to placebo, baclofen treatment resulted in a slightly deleterious effect on mTFC, but the magnitude of the effect with respect to the standard error was not significant. Older age (≥ 35 years) compared with younger age (< 35 years) and stage II compared with stage I subjects showed slightly beneficial effects on mTFC, but never at a 0.05 level of significance. Decline in mTFC at 30 months was nonsignificantly greater for subjects with paternal inheritance of the HD gene in comparison with subjects with maternal inheritance (−0.55, and 0.40 for estimate and standard error of the effect).

Table 4 summarizes the rate of mTFC decline, comparing actual values for baseline evaluation and evaluation at 30 months unadjusted for age, stage, treatment, or mode of inheritance. The annual rate of change in mTFC for the baclofen group was 0.85 ± 0.64 units/year compared with 0.53 ± 0.46 units/year for the placebo group, and these differences approached significance (t = 1.996, p = 0.053). When the influences of age, stage, and inheritance were included in the analysis, the effect of baclofen on change in mTFC was *not* significant (t = 0.61/0.40 = 1.53, p = 0.14).

Effect of Mode of Inheritance of HD

Inheritance of the HD gene from an affected father has been linked to earlier onset of illness in comparison with onset in HD patients who inherit the gene from an affected mother [38, 39]. Randomization to experimental drugs was not stratified according to mode of HD gene inheritance. While there were no significant differences between treatment groups at entry with respect to age or duration of illness (see Table 2), the baclofen-assigned subjects showed a nearly 2:1

Table 4. mTFC Averaged among Seven Raters, Comparing Baseline Value to Value at 30 Months, Unadjusted for Age, Stage, Treatment, or Mode of Inheritance[a]

Group	mTFC Units at Baseline	mTFC Units at 30 Months	Change in mTFC Units (30 mo − baseline)	Change in mTFC Units/Year (30 mo − baseline)
Placebo (n = 26)	10.00 ± 1.70	8.68 ± 2.31	−1.32 ± 1.16	−0.53 ± 0.46
Baclofen (n = 23)	10.75 ± 1.39	8.62 ± 1.81	−2.13 ± 1.61	−0.85 ± 0.64
Overall (n = 49)	10.35 ± 1.59	8.65 ± 2.07	−1.70 ± 1.43	−0.68 ± 0.57

[a]Values are expressed as the mean ± standard deviation.

mTFC = mean total functional capacity.

Table 5. Inheritance Effects on mTFC at Baseline and 30 Months (total n = 49)[a]

Group	mTFC at Baseline	mTFC at 30 Months	Decline Between Baseline and 30 Months in mTFC Units/Year
Overall maternal (n = 21)[b]	10.26 ± 1.63	8.97 ± 2.00	0.52 ± 0.52
Overall paternal (n = 28)[b]	10.42 ± 1.60	8.40 ± 2.13	0.81 ± 0.59
Placebo maternal (n = 13)[c]	10.25 ± 1.68	9.32 ± 2.13	0.37 ± 0.33
Baclofen maternal (n = 8)[d]	10.27 ± 1.62	8.41 ± 1.72	0.74 ± 0.69
Placebo paternal (n = 13)[c]	9.75 ± 1.75	8.02 ± 2.39	0.69 ± 0.53
Baclofen paternal (n = 15)[d]	11.00 ± 1.23	8.73 ± 1.91	0.91 ± 0.63

[a]Values are expressed as the mean ± standard deviation.
[b]Overall maternal versus paternal: $t = 1.80$, $p = 0.08$.
[c]Maternal placebo versus paternal placebo: $t = 1.78$, $p = 0.09$.
[d]Maternal baclofen versus paternal baclofen: $t = 0.57$, $p = 0.58$.

mTFC = mean total functional capacity.

predominance of paternal descent of the HD gene in comparison with the 1:1 ratio of paternal to maternal inheritance among placebo subjects. Including mode of inheritance in our analysis of variance model (i.e., mTFC = age + stage + treatment + inheritance) reduced the influence of baclofen treatment and made nonsignificant the deleterious effect of baclofen as judged by Rater 4 (see Table 3). The overall effect of considering mode of inheritance in the model was to reduce the t statistic for the baclofen effect from 1.70 (0.68/0.40) to 1.53 (0.61/0.40).

Table 5 compares mTFC at baseline and at 30 months for the 21 subjects with maternal HD inheritance and the 28 subjects with paternal HD inheritance. Regardless of treatment, those with maternal inheritance declined at 0.52 ± 0.52 (mean ± SD) TFC units/year compared with subjects with paternal inheritance, who declined at a rate of 0.81 ± 0.59 TFC units/year ($t = 1.80$, $p = 0.08$). An accelerated rate of TFC decline for subjects with paternal inheritance was observed for both baclofen and placebo groups, but the differences were not significant ($p = 0.09$ for placebo, $p = 0.58$ for baclofen). The magnitude of treatment and inheritance effects each accounted for approximately 6% of the variance. Although the majority of the variance was attributable to residual unaccounted factors, such as subject and rater variability, the effect of HD gene inheritance was on the same order of magnitude as the influences of age, stage, and treatment.

Adverse Effects

Surveillance monitoring of adverse effects at 6 to 12 month intervals showed no significant treatment differences with respect to a wide range of symptoms (drowsiness, dizziness, weakness, fatigue, headache, confusion, burning numbness, muscle cramps, ringing in the ears, slurred speech, incoordination, shaking, blurred vision, double vision, sleep disturbances, depression, euphoria, hallucinations, palpitations, chest pain, nausea, constipation, loss of appetite, abdominal pain, diarrhea, urinary frequency/hesitancy, rash, itching) and laboratory tests (complete blood count, blood urea nitrogen, glucose, creatinine, alkaline phosphatase, bilirubin, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase).

Effect of Washout

Self-rating data regarding sense of well-being were analyzed for subjects who underwent the 4-week washout of experimental drugs. At 1 week, those who discontinued placebo reported overall slight worsening (−0.50 ± 1.55 units, mean ± SD) in comparison to the slight improvement (+0.13 ± 1.25) reported by those who discontinued baclofen. By 4 weeks, subjects in both treatment groups felt worse (−0.69 ± 1.30

for placebo, −0.87 ± 2.64 for baclofen) in comparison to the day before beginning washout. These differences were not significant, and withdrawal symptoms were not observed.

Assessment of Blindness of Study

Forty-five of the 49 subjects provided their guesses concerning experimental treatments after conclusion of the trial. Of 25 subjects who actually received placebo, 9 guessed that they were taking placebo, while 16 guessed that they were taking baclofen. Of the 20 subjects who actually received baclofen, 4 guessed placebo and 16 guessed baclofen. Guesses by chaperons were 50% accurate for placebo and 60% accurate for baclofen. Guesses for the seven blinded raters ranged from 41 to 72% accuracy for both treatments, with average accuracy of 49.5% for placebo and 50.7% for baclofen. There were no significant differences in accurate guesses for subjects ($\chi^2 = 1.39$, $p = 0.239$), chaperons, or raters.

Discussion

The results indicated that baclofen, 60 mg/day, for at least 30 months did not favorably influence the progression of early HD as measured by TFC. Baclofen did produce a slight but nonsignificant effect in hastening TFC decline in comparison to the decline experienced by the placebo-treated patients. This trend may have been related in part to clinical and subclinical adverse effects of baclofen, as observed in 3 subjects who clearly developed increased involuntary movements and 2 who became psychotic, and in part to the slight subjective improvement reported initially during washout of the baclofen-treated subjects. Variables that tended to contribute to a more rapid functional decline—including younger age, earlier stage, and paternal HD transmission—occurred more frequently among the baclofen group. While it is possible that baclofen may have adversely influenced the underlying neurobiological course of HD, such a deleterious effect must have been very small and not adequately detected by our sample size.

In any event, our findings do not in any way support a protective action of baclofen for patients in the early stages of HD. Rather, our results caution that the reported short-term beneficial effects of baclofen [20–22] may not be enduring and may possibly be attended in the longer term by more rapid functional decline. This concern also applies to the apparent short-term symptomatic benefits of other medications thought to help HD, including the neuroleptic antichoreic drugs.

Younger age (< 35 years) at entry and earlier stage (stage I) illness were stratification variables that accounted for a nonsignificant effect in hastening the decline of mTFC. In addition, subjects with paternal inheritance of the HD gene, regardless of age at onset of illness or age at entry, tended to decline faster than those with maternal inheritance. This tentative relationship implies that the deleterious genetic effect of paternal HD inheritance is manifested eventually by a more malignant course of illness (pace of neuronal degeneration) as well as earlier onset (clinical threshold of neuronal loss). Our findings suggest also that parental descent of the HD gene should be considered as a stratification factor for randomization in future trials.

Notwithstanding treatment, the HD patients in our clinical trial progressed at a considerably slower rate of functional decline, averaging about 0.7 TFC units/year overall (see Table 4), than that reported in other prospective studies. In 1981, Shoulson reported a TFC decline of 1.8 units/year among 22 HD patients who were treated largely with neuroleptics [24]. More recent observations in a group of neuroleptic-free HD patients show an average rate of TFC decline between 1.0 and 1.25 units/year (Shoulson and Behr, unpublished observations). Data from largely untreated HD patients followed longitudinally for up to 7 years in the United States–Venezuela Cooperative Huntington's Disease Project show an average TFC decline of about 1.0 unit/year among all patients and a faster rate of about 1.7 units/year in patients with early HD [33]. Had we relied solely on these observational studies as historical controls rather than a prospective randomized trial, we would have concluded erroneously that baclofen favorably influenced early HD by slowing functional decline to a rate of 0.85 TFC units/year. In fact, baclofen was not better than placebo and possibly was worse.

The considerably slower rate of TFC decline in both our baclofen- and placebo-treated subjects may be related to the following: (1) our eligibility criteria, which excluded subjects who had serious illness or psychopathological findings and who were therefore not considered able to complete the trial; (2) avoidance of neuroleptic therapy; (3) general nurturing and support that our subjects received throughout the trial; and (4) restriction of supplemental monosodium glutamate. We suspect that the first three factors strongly influenced the slower rate of functional decline in our subjects. It is unclear whether dietary restriction of monosodium glutamate had any salutary effect upon the course of HD.

The prospectively derived data from the trial provided some insights regarding future clinical trials involving protective strategies for HD. Assuming a standard deviation of 1.5 TFC units in each treatment group, we estimated power for detecting minor and major therapeutic effects of 0.48 and 0.93, respectively. In actuality (see Table 4), 49 subjects were followed to 30 months with a total difference in mTFC of 0.81 units (2.13 − 1.32) unfavorable to baclofen, and standard deviations of 1.61 for baclofen (n = 23) and 1.16 for placebo (n = 26). After allowance for age, stage, and mode of HD inheritance, the estimated

Table 6. Estimates of Sample Size Requirements Using Actual Differences in mTFC Observed in Placebo-Treated Subjects[a]

Group	Major Therapeutic Effect (40% reduction in mTFC)		Minor Therapeutic Effect (20% reduction in mTFC)	
	Power 0.80	Power 0.90	Power 0.80	Power 0.90
18-month follow-up: change in mTFC ± SD = 0.79 ± 0.90	250	334	996	1,332
30-month follow-up: change in mTFC ± SD = 1.32 ± 1.16	152	204	628	840
42-month follow-up: change in mTFC ± SD = 2.32 ± 1.30	64	84	252	338

[a]Sample size is estimated for total number of subjects (control and treatment) required (without allowance for dropouts) for powers of 0.80 and 0.90, using a two-sided, two-sample Student's t test with a significance level of 0.05.

mTFC = mean total functional capacity; SD = standard deviation.

mean difference was 0.61 with standard error 0.40, giving a nonsignificant t value of 1.53. Since the study was designed with a one-sided test of significance to detect only beneficial effects, a statistically significant harmful effect of baclofen could not have been detected with our sample size, no matter how extreme the observed difference. A post-hoc power calculation based on 49 subjects (23 on active drug, 26 on placebo), carried out for an intervention that reduces the observed 30-month decline of 1.32 TFC units by 40% (or 20% for a minor effect) while leaving the standard deviation unchanged at 1.16, provides power of only 0.34 (or 0.11).

In view of the actual outcome of our study, we can draw several conclusions regarding the design and conduct of a controlled clinical trial aimed at slowing the rate of functional decline in HD. In spite of pilot data or reports suggesting symptomatic benefits, a two-sided test of significance (and a resultant loss of power) is required for protective trials in HD. In other words, efforts to influence the underlying neuropathogenesis of HD are fraught with hazards of accelerating neuronal degeneration and clinical decline. This caution may also apply to experimental protective strategies for other neurodegenerative diseases.

Although TFC decline provides a clinically meaningful response variable that has high reliability among practiced raters and validity with respect to computed tomographic indexes of caudate atrophy, the relatively slow rate of observed change in TFC requires sample sizes several times greater than the 60 subjects we studied. Using the actual differences in TFC observed in our placebo-treated subjects, sample size could be reestimated for 0.80 and 0.90 power (Table 6). Depending on the estimated magnitude of the therapeutic effect, we would have required sample sizes up to 20 times greater than studied to achieve an acceptable likelihood of detecting the effect. This sample size reanalysis also suggests that power is enhanced by increasing the duration of follow-up, but extending the period of observation may be achieved at the expense of further dropouts as well as a resulting loss of power.

To minimize the number of dropouts, we selected patients in early HD who did not have serious motor or mental illness requiring pharmacotherapy with neuroleptics or antidepressants. In so doing, we also selected patients who likely had a slower rate of functional decline than the general HD population. This highlights a problem in designing protective trials for HD that employ change in some relevant clinical or neurobiological measure of disease as the major response variable. As one selects out mildly progressive illness to minimize dropouts, the expected magnitude of change lessens. One approach to overcoming this problem is the design of trials using survival or failure time as the major response variable [40]. As applied to HD, following selected individuals at risk for HD until gene carriers first manifest signs of disease might provide a more powerful design to test promising protective interventions.

To the extent that baclofen attenuated corticostriatal excitatory neurotransmission at the dosage administered to our patients, it is unlikely that a strategy of retarding presynaptic release of glutamate and aspartate will protect against the postsynaptic striatal degeneration and clinical decline of HD. It is recognized that glutamate subserves many neural functions and at least three receptor subtypes. The NMDA glutamate receptor has been increasingly implicated as a target and perhaps a mediator of neuronal degeneration in HD [41, 42], and NMDA receptor antagonists exert potent protective effects in vitro and in animal models of HD [10, 43, 44]. The findings and experience generated from our controlled clinical trial of baclofen should help in designing studies to test these and other promising interventions for HD.

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