BROMOCRIPTINE IN THE TREATMENT OF POST-POLIO FATIGUE:
A pilot study with implications for the pathophysiology of fatigue.

Richard L. Bruno, Ph.D.,[1 2] Jerald R. Zimmerman, M.D.,[1 2] Susan Creange, M.A.,[1] Todd Lewis, Ph.D.,[1] Terry Molzen, M.A.,[1] and Nancy M. Frick, M.Div, Lh.D.[3]

American Journal of Physical Medicine and Rehabilitation, 1997 (in press)

1. Post-Polio Rehabilitation and Research Service
   Kessler Institute for Rehabilitation
   East Orange, New Jersey
2. Department of Physical Medicine and Rehabilitation
   UMDNJ/New Jersey Medical School
   Newark, New Jersey
3. Harvest Center
   Hackensack, New Jersey

Address all correspondence and reprint requests to:
Dr. Richard L. Bruno,
Post-Polio Rehabilitation and Research Service,
Kessler Institute for Rehabilitation,
300 Market Street,
Saddle Brook, New Jersey 07662.
(201) 368-6057

This research was supported by grants from the George Ohl, Jr. Infantile Paralysis Foundation, Sandoz Pharmaceuticals, The Joel Leff Charitable Trust, and the Deluxe Corporation.

Short Title: Bromocriptine and Post-Polio Fatigue

ABSTRACT

Objective: Determine the effectiveness of bromocriptine in the treatment of severe and disabling post-polio fatigue.
Design: Placebo-controlled drug trial in a pilot series of patients.
Setting: Outpatient rehabilitation hospital.
Patients: Of 83 patients without comorbidities who completed treatment with the Post-Polio Service, 5 of 8 patients who had paralytic polio and continued to report moderate to severe daily fatigue after complying with conservative treatments for post-polio fatigue agreed to be studied.
Intervention: Placebo was given for four weeks followed by increasing doses of bromocriptine mesylate (Parlodel®) administered at noon for 28 days reaching a total dose of 12.5 mg/day.
Main Outcome Measures: Daily logs of subjective fatigue and cognitive difficulties.
Results: Three of the subjects reported symptom improvement on bromocriptine but not on placebo. However, all subjects experienced nausea on bromocriptine, likely eliminating blinding. Drug responders had clinically impaired performance on neuropsychological tests of attention and information processing speed. Logged daily difficulty with attention, cognition, word finding memory, staying awake and fatigue on awakening were significantly negatively correlated with days on bromocriptine, but not with days on placebo, in drug responders.
Conclusions: A double-blind, placebo-controlled multicenter study will be needed to confirm bromocriptine's effectiveness in treating attentionally-impaired polio survivors whose severe and disabling fatigue does not responded to conservative treatment.

Key Words: Bromocriptine; Dopamine; Polio; Post-Polio Sequelae; Fatigue; Attention

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BROMOCRIPTINE IN THE TREATMENT OF POST-POLIO FATIGUE: A pilot study with implications for the pathophysiology of fatigue.

Fatigue is the most commonly reported and most debilitating Post-Polio Sequelae (PPS) affecting the more than 1.63 million American polio survivors. *[1]* In national surveys of polio survivors, 91% reported new or increased fatigue, 41% reported fatigue significantly interfering with performing or completing their work and 25% reported fatigue interfering with self-care activities. *[2,3]* Importantly, polio survivors differentiate between physical tiredness that they associate with new muscle weakness or decreased endurance, and a "brain fatigue" that is characterized by fatigue plus difficulties with attention and cognition. Between 70% and 96% of polio survivors with fatigue reported concomitant problems with concentration, memory, attention, word-finding, maintaining wakefulness and thinking clearly, with 77% percent reporting moderate to severe problems with these functions. *[3]* On formal neuropsychological testing, only polio survivors reporting severe daily fatigue demonstrated clinically significant deficits of attention, concentration and information processing speed. *[4]* It has been hypothesized that both subjective fatigue and attention deficits in polio survivors result from poliovirus damaging neurons within the brain's activating system. *[3]* Postmortem studies of 50 years ago demonstrated the consistent presence of poliovirus lesions in the midbrain reticular formation, posterior hypothalamus, thalamic nuclei, putamen and globus pallidus. *[3,5]* Recently, magnetic resonance imaging of the brain has shown small discrete or multiple punctate areas of hyperintense signal in the reticular formation, thalamic and caudate nuclei, putamen, centrum semiovale, deep and periventricular white matter only in polio survivors reporting fatigue. *[3,6]* Postmortem histopathology also found that neurons secreting neurotransmitters

known to activate the brain, especially dopaminergic neurons in the substantia nigra, were also damaged or destroyed by the poliovirus. *[5,7]* The reduced secretion of dopamine has been hypothesized to play a role in impairing polio survivors' ability to activate the cortex, thereby generating difficulty with attention, concentration and maintaining wakefulness that polio survivors described as "brain fatigue." *[7]* The hypothesized role of the basal ganglia and dopamine in activating the brain suggests that a dopamimetic agent would be the most promising candidate to pharmacologically treat brain fatigue. *[7]* However, any dopamimetic agent employed to treat fatigue should not stimulate (as do amphetamines and methylphenidate) nor require the functioning of (as do L-Dopa, monoamine reuptake blockers and monoamine oxydase inhibitors) the remaining poliovirus-damaged neurons in the brain's activating system. Therefore, bromocriptine mesylate (Parlodel ®; Sandoz), a direct-acting, post-synaptic dopamine 2 (D2) receptor agonist, was chosen for a placebo-controlled study of a pharmacological treatment for post-polio fatigue.

METHODS

Subjects. Only patients who were without comorbidities that could cause fatigue or cognitive problems (e.g., psychiatric diagnoses, thyroid, cerebrovascular or cardiac disease, anemia, respiratory insufficiency, sleep apnea or hypopeneas, lupus or diabetes) and who successfully completed treatment for PPS were eligible for the drug trial. Of eighty-three patients who met these criteria, only ten continued to report at least moderate daily fatigue (the fatigue level required for inclusion in the study) after applying the conservative treatments of choice for post-polio fatigue, i.e., reducing physical and emotional stress, using appropriate assistive devices, energy conservation, adequate rest and the pacing of activities. *[8,9,10]* Of those ten, two met DSM-III-R criteria for a major depressive episode and were excluded. *[11]* Of the remaining eight patients, six agreed to the drug trial. One patient withdrew after her husband was severely injured in a fall, leaving five patients to be studied.

Procedure. Fatigue research is methodologically problematic since fatigue is subjective and therefore difficult to quantify. This problem is compounded by polio survivors' difficulty acknowledging, let alone quantifying, their physical symptoms and the variability of their fatigue, both within and between days. *[8]* Therefore, all subjects gave written informed consent and completed a modified version of the Post-Polio Fatigue Questionnaire (PFQ) for 14 days prior to beginning drug, rating subjective levels of fatigue five times during the day and rating daily and difficulty with motivation, attention, mind wandering, thinking clearly, concentration, word finding, object naming, memory, staying awake during the day, and muscle weakness on a six-point scale from "none" through "severe." *[3,4]* All but one subject who was severely claustrophobic had magnetic resonance imaging (MRI) of the brain which were read by a radiologist blinded to the subjects symptoms (see 6). On another occasion, plasma ACTH was drawn at 11:00 AM after an overnight fast. (see 7) On the 15th day, blood was drawn at 10:00 AM for a complete blood count, chemistry, thyroid panel and plasma prolactin. Neuropsychological tests that assessed attention, concentration and information processing speed were then administered by a blinded examiner. The Double Letter Cancellation Test required subjects to cross-out two specified letters on a sheet filled with similar letters in the shortest possible time to assess selective and sustained attention. *[12]* The Gordon Diagnostic Systems continuous performance test, measuring focused and sustained attention, required subjects to watch numbers presented for 6 minutes on a 1 by 2 cm. LED display. *[13]* subjects were instructed to press a button only when the number "9" appeared immediately following the number "1" while two flanking LED displays also presented numbers including "9" and "1" (distractibility task) and while the flanking displays were dark (vigilance task). The Trail Making Test assessed visual scanning and visual motor speed by requiring subjects to draw a line to sequentially connect circles containing 25 ascending numbers (Part A) or sequentially but alternately connect circles containing ascending numbers and the letters of the alphabet (Part B) in the shortest possible time. *[14]* The Paced

Auditory Serial-Addition Test (PASAT) assessed complex attention and information processing speed by requiring subjects to sequentially add a series of 60 digits presented by a tape recording at three presentation speeds: one digit every 1.6, 2.0 and 2.4 seconds. *[15]* All neuropsychological tests were administered and scored according to accepted procedures.

Placebo/Drug Administration. The 14 days of pre-testing PFQs were reviewed with the subjects to determine that they understood how to rate and log their symptoms. Subjects were told that they would receive either placebo or a drug which it was hoped would reduce their fatigue symptoms. They were given 28 daily log forms and instructed to rate their fatigue upon awakening, at 12:00, 3:00, 6:00 and 9:00 PM. Subjects were instructed to describe any side effects experienced during the day and rate their overall difficulty with the subjective symptoms listed on the PFQ at 9:00 PM. Since bromocriptine almost invariably causes nausea, all subjects received placebo first. Subjects were given 10 numbered bottles, each containing three opaque capsules, and instructed to start with bottle number one and to take one capsule each day during the noon meal. Every three days, they would open the next higher-numbered bottle and take one capsule at noon. Subjects were unaware that they were receiving a cornstarch placebo during the first 28 study days. After 28 days on placebo, subjects were re-administered the neuropsychological tests, given another set of log forms, bottles with identical capsules and told to continue taking the capsules as they had been. Subjects began with 1.25 mg/day of bromocriptine and increased the dose by 1.25 mg every three days, reaching a total daily dose of 12.5 mg. After 28 days on bromocriptine, subjects were readministered the neuropsychologic tests and had blood drawn for bromocriptine plasma level and plasma prolactin, which is suppressed by the administration of dopamine receptor agonists.

Data Analysis. Since the small sample size prevented statistical comparisons, subjects' individual measurements and group means were compared to established clinical norms to determine whether the physiological variables or neuropsychologic test performance were clinically abnormal. (Table 1) SYSTAT (Version 6.0) was used to calculate product-moment correlations and linear regressions for daily fatigue and symptom difficulty ratings with days on placebo and bromocriptine for each individual subject. *[16]* Correlations were transformed to z scores, averaged across subjects, and then transformed back to correlations. *[17]* (Table 2) Because the large number of variables being correlated increased the probability of obtaining significant correlations by chance, the Bonferroni inequality was applied to decrease the probability (p) value needed for significance by dividing the p value by the number of variables being correlated. The regression equations were used to calculate the fatigue and symptom difficulty rating for each drug responder for the last day on placebo (day 28) and on bromocriptine (day 56). The mean calculated fatigue and symptom difficulty ratings are shown in Figure 2.

RESULTS

Demographics. Subjects (3 female; 2 male) were 49 (± 2.1) years old having had paralytic polio at age 5 (± 2.6) in 1949 (± 2.4) and 15 (± 3.0) years of education. One subject had been a diplegic wheelchair user since polio. The others had ambulated for 35 years without assistance before the onset of new muscle weakness; 3 were prescribed a straight cane and one a molded ankle/foot orthosis when treated for their PPS. Subjects rated their current daily fatigue as moderate to severe. Four subjects were retired on Social Security disability as a result of fatigue preventing continued employment; the remaining subject worked part-time as a secretary.

Drug Response: Neuropsychological Testing. Three subjects reported a noticeable reduction in fatigue and related cognitive symptoms on bromocriptine as compared to placebo. Drug responders reported that they "felt awake" and "had a clear head" for the first time in several years. Two subjects reported no effect at

all on bromocriptine or placebo. There were clinically significant differences in baseline measures between drug responders and non-responders (Table 1). There were more than twice as many areas of hyperintense signal on MRI of the brain on average in the drug responders. Fasting ACTH was abnormal in all of the drug responders in that it was not elevated above the baseline value expected for non-fasting subjects at 11:00 AM. *[7]* A clinically significant increase in mean ACTH was seen in the non-responders, one of whom had a normal elevation in fasting ACTH. The baseline mean plasma prolactin level was nearly doubled in the drug responders, suggesting reduced brain dopamine activity. In the drug responders, the lower mean number of correct responses at baseline on the Gordon distractibility and vigilance tests and on the 2.4 numbers/second presentation of the PASAT were clinically abnormal, as was the longer time required to perform the Trail Making Test (Part A). Scores on all neuropsychological measures in all subjects moved toward or reached normality with repeated testing on placebo and then on bromocriptine. Prolactin decreased from 11.2 (± 6.2) ng/ml at baseline to 3.2 (± 4.0) ng/ml on bromocriptine as would be expected with a dopamine receptor agonist. The plasma level of bromocriptine was below the detectable range in all subjects.

Drug Response: Symptom Logs. In the drug responders, the rating of fatigue upon awakening and difficulty with attention, word finding, mind wandering, concentration, remote memory, thinking clearly decreased and were significantly negatively correlated with days on bromocriptine, but not with days on placebo (Figure 2; Table 1). These ratings decreased by about one grade, from above "mild to moderate" to "mild" (Figure 2). Fatigue decreased from about "moderate" to "mild to moderate," with fatigue upon awakening decreasing most (55%). Subjective muscle weakness did not change on bromocriptine or on placebo. In the drug non-responders, difficulty with word finding, memory, and object naming were significantly positively correlated with days on bromocriptine. However, fatigue at noon and 9:00 PM and muscle weakness were significantly positively correlated with days on placebo. Nevertheless, the non-responders did not complain of an increase in any of these symptoms during either phase of the study.

Side Effects. The most common complaint was a low-grade nausea that is the most frequently reported side-effect of bromocriptine. All subjects reported nausea for from 2 to 10 days (a mean of 28% days) on bromocriptine. Two subjects reported nasal fullness, one for 9 days and another for 2 days, for a mean of 20% of the days on bromocriptine. The latter subject also reported a daily dull headache on bromocriptine that may have been related to nasal fullness. However, no subject discontinued bromocriptine because of these side effects. At the highest dose of bromocriptine, one subject did have an episode of severe nausea, followed by six brief episodes of syncope with high-grade atrioventricular block when she attempted to vomit. While this subject had only two previous episodes of mild nausea on bromocriptine, she did have a life-long history of syncope during vomiting. Although cardiodepressor syncope was not a previously known side effect of bromocriptine, the drug was discontinued.

DISCUSSION

This pilot study of severely fatigued polio survivors suggests that bromocriptine may be of use in the treatment of post-polio fatigue that has not responded to conservative therapies. However, the small sample size and methodological limitations make this suggestion merely tentative. Since nausea was universally experienced, all subjects may have realized that they were receiving active drug and were thereby biased toward reporting reductions in symptoms. The percentage of days on which side effects were experienced on bromocriptine was higher in the responders (48%) than non-responders (34%). Although the placebo phase was not compromised, the bromocriptine phase of the study may have been as unblinded as an open-label drug trial. Reductions in morning fatigue and fatigue-related cognitive symptoms as the dose of bromocriptine increased were not paralleled by drug-related improvements in neuropsychologic test scores, most likely since the same form of the tests was administered on placebo

and on bromocriptine. Subjects repeatedly taking the same test would be expected to demonstrate a learning effect and have their test scores improve. This has been seen even in polio survivors with severe fatigue who were repeatedly administered the same neuropsychologic tests over the course of several hours *[4]* It was also surprising that drug responders noticed no reduction in fatigue during the afternoon, since bromocriptine was administered at noon so that a peak blood level would be reached at 3:00 PM when many polio survivors report hitting an afternoon "wall" of fatigue. Since the pharmacokinetics of bromocriptine could differ from the time course of its pharmacological effect, as is seen with D2 receptor antagonists, moving the dose of drug to before sleep or upon awakening may prolong any beneficial effect of the drug into the afternoon. *[18]*

A Central or Peripheral Pathophysiology of Fatigue? Several other agents have been studied in an attempt to treat post-polio fatigue. In placebo-controlled studies, high-dose prednisone and amantadine, a drug with anticholinergic and dopamimetic properties, did not decrease fatigue. *[19,20]* An open-label trial of pyridostigmine was conducted in 25 polio survivors whose fatigue had not responded to conservative treatments. *[21]* After at least one month on drug, 64% of subjects reported a 56% decrease in "general fatigue," a finding comparable to the 55% decrease in morning fatigue in 60% of the subjects in this study. The authors concluded that although the subjective complaint of fatigue has multiple causes, it was reduced in their subjects by pyridostigmine enhancing conduction at the neuromuscular junction and thereby increasing muscle strength and decreasing muscle fatiguability. Since bromocriptine reduced morning fatigue and fatigue-related cognitive symptoms, but had no effect on subjective muscle weakness, it is likely acting centrally to stimulate dopaminergic receptors within the brain's activating system. This conclusion is supported by a placebo-controlled study of healthy subjects who were administered remoxipride, a potent and selective D2 receptor antagonist. *[18]* The most frequently reported effects of D2 receptor blockade were "moderate fatigue," "mild somnolence" and "difficulty concentrating." Statistically significant, dose-related increases in subjective "drowsiness" and impairment on neuropsychological tests of auditory vigilance, continuous attention and critical flicker fusion wer also found following D2 receptor blockade. However, decreased neuromuscular junction transmission impairing muscle contraction and decreased attention resulting from impaired brain activation are not mutually exclusive causes of post-polio fatigue. The contribution of both muscle weakness and impaired attention to the complaint of fatigue was documented by administering the Post-Polio Fatigue Questionnaire as part of the 1990 National Post-Polio Survey. *[3]* Multiple regression revealed that the only significant contributors to the prediction of daily fatigue severity were "difficulty focusing attention" ($r=0.31$; $p=.005$) and "muscle weakness" ($r=0.19$; $p=.023$). Actually, there may be an interaction between impaired transmission at the neuromuscular junction, decreased brain activation and symptoms of fatigue. As early as 1939, muscle spindle afferent activity was recognized as important in the maintenance of "alertness." *[22]* Neuromuscular transmission blockade, which eliminated muscle activation and thereby afferent muscle spindle discharges, was shown to inhibit the ascending reticular activating system, decrease cortical activation, cause "drowsiness" and even induce a level of anesthesia sufficient for surgery. *[23,24,25]* Further, the relaxation and reduced recruitment of motor units have been identified as peripheral signs of central fatigue, possibly resulting from a decrease in the activity of the descending reticular activating system. *[26,27]*

Clinical Application and Caveats. These very preliminary findings suggest that bromocriptine may be helpful in treating polio survivors whose fatigue is more central in origin (i.e., associated with impaired attention and cognition) while pyridostigmine may be helpful in treating patients whose fatigue is more peripheral (i.e., associated with muscle weakness, fatiguability or decreased physical endurance). Responders to pyridostigmine had higher fatigue ratings at baseline, while drug responders in this study had clinically significant impairments of attention and information processing speed, more hyperintensities on MRI, an absent ACTH response to stress and increased plasma prolactin. Taken

together, these data suggest that any medication for post-polio fatigue will benefit only the most fatigued, neuropsychologically impaired or neurophysiologically abnormal patients who have not responded to conservative therapies. This conclusion is underscored by the experience with the drug non-responders. One was the least impaired of the subjects, reporting moderate to severe daily fatigue, having two hyperintensities on MRI, scores on only two of the attention tests that fell just below the normal range, and being the only subject able to work, albeit part-time. The other non-responder reported severe daily fatigue, had one punctate hyperintensity in her rostral reticular formation on MRI, but had no abnormalities on neuropsychological testing. However, her daily logs revealed that she was applying none of the conservative treatments that had been recommended. She neither paced her activities nor rested during the day. She went to sleep after midnight on 87% of the study days, compared to a mean of 26% of study days for the other subjects. Following the study, she modified her schedule and her daily fatigue decreased from severe to moderate to severe without the use of medication. This subject's inability to implement the lifestyle changes necessary to treat her fatigue may be responsible for the positive correlations between days on placebo, fatigue, cognitive symptoms and muscle weakness in the non-responders. Polio survivors' frequent non-compliance with fatigue-reducing lifestyle changes is well described. *[8,28]* However, medication is not a substitute for self-care and no medication to treat post-polio fatigue should be prescribed until all conservative therapies have been consistently applied by the patient and found inadequate to reduce fatigue sufficiently to allow a satisfactory level of personal, vocational and recreational functioning.

Future Research. The finding that only 10% of compliant patients without comorbidities reported moderate or greater daily fatigue after treatment by the Post-Polio Service is hopeful, indicating that conservative therapies appear to be successful in treating most polio survivors' fatigue. However, the success of non-pharmacological therapies makes difficult identifying a sufficiently large sample of appropriate subjects at any one facility. Clinician/researchers thoroughly familiar with treating polio survivors and PPS at a number of post-polio clinics will be needed if a sufficiently large sample is to be recruited for a double-blind, placebo-controlled, cross-over study of the efficacy of bromocriptine in the treatment of severe, treatment-resistant post-polio fatigue. Since nausea was reported by all subjects, domperidone - a dopamine receptor antagonist that does not cross the blood-brain barrier and has been shown to counteract the nausea caused by dopamimetics in Parkinson's patients without decreasing bromocriptine's efficacy - could be given with bromocriptine to allow a blinded, cross-over design. *[29]* However, the safety of bromocriptine remains a concern. Given the association of nausea and syncope in one subject, dopamimetics may be contraindicated in polio survivors with a history of syncope or even in those with bulbar polio that damaged brain stem cardioregulatory centers. *[30,31,32]* Also, the long-term effects of dopamimetic agents in polio survivors have not been studied. Receptor down-regulation and the development of tolerance with the chronic use of a D2 receptor agonist is a possibility. Down-regulation occurs with negative clinical consequences following chronic use of dopamimetics in Parkinson's disease patients. *[33,34,35]* Bromocriptine-induced receptor down-regulation could actually increase fatigue by combining with reductions in D2 receptor number and the level and activity of dopamine-synthetic enzymes in the nigra and putamen that accompany aging. *[36,37]* These reductions, thought to occur "due to impairment of cellular regulatory systems or to decreased presynaptic dopamine input" resulting from attrition of dopaminergic neurons, may be accelerated in polio survivors and have been implicated in the pathogenesis of fatigue as polio survivors reach midlife. *[3,7,27]* On the other hand, it has also been suggested that dopamine receptor agonists may exert a "protective action" on poliovirus-damaged, metabolically impaired dopaminergic neurons since they reduce the demand for pre-synaptic dopamine production. *[3,38]* Reduced dopamine production would decrease neurons' internal metabolic requirements and lower oxidative stress by limiting the amount of hydrogen peroxide formed by the action of MAO-B. *[38]* Thus, administration of bromocriptine may not only potentially decrease symptoms of brain fatigue but also could possibly slow the metabolic failure of the remaining poliovirus-damaged

dopaminergic neurons. *[39]* Future studies will need to address these concerns as well as objectively document fatigue's peripheral and central symptoms and signs if the pathophysiology of fatigue, location of drug action, and drug efficacy and safety are to be determined.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the participation of the subjects, the continuing support of the George Ohl, Jr. Infantile Paralysis Foundation, Sandoz Pharmaceuticals for providing the bromocriptine, and the efforts and expertise of Doris Sipos, Carol Diveny and Mary Ann Solimine, R.N., M.L.S., with out whom this work would not have been possible. We also thank Jim Schoen, R.P., M.B.A. for preparing and packaging bromocriptine and placebo, Joan Alverzo, R.N. for monitoring side effects in some of the patients, and Dr. Oliver Sacks for his comments.

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Top of Article

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Document preparation: Chris Salter, Original Think-tank, Cornwall, United Kingdom.
Document Reference: <URL:http://www.zynet.co.uk/ott/polio/lincolnshire/library/harvest/bromo.html>
Created: January 1997
Last modification: 29th January 2010.