Pyridostigmine in postpolio syndrome: no decline in fatigue and limited functional improvement


Objective: To investigate the effect of pyridostigmine on fatigue, physical performance, and muscle function in subjects with postpoliomyelitis syndrome.

Methods: 67 subjects with increased fatigue and new weakness in one quadriceps muscle showing neuromuscular transmission defects, were included in a randomised, double blind, placebo controlled trial of 60 mg pyridostigmine four times a day for 14 weeks. Primary outcome was fatigue (on the ‘’energy’’ category of the Nottingham health profile). Secondary outcomes included two minute walking distance and quadriceps strength and jitter. Motor unit size of the quadriceps was studied as a potential effect modifier. The primary data analysis compared the changes from baseline in the outcomes in the last week of treatment between groups.

Results: 31 subjects treated with pyridostigmine and 31 subjects treated with placebo completed the trial. No significant effect of pyridostigmine was found on fatigue. The walking distance improved more in the pyridostigmine group than in the placebo group (by 7.2 m (6.0%); p<0.01). Subgroup analysis showed that a significant improvement in walking performance was only found in subjects with normal sized motor units. Quadriceps strength improved more in the pyridostigmine group than in the placebo group (by 6.7 Nm (7.2%); p=0.15). No effect of pyridostigmine was found on jitter.

Conclusions: Pyridostigmine in the prescribed dose did not reduce fatigue in subjects with postpoliomyelitis syndrome. However, it may have a limited beneficial effect on physical performance, especially in subjects with neuromuscular transmission defects in normal sized motor units.
lateral vastus were recorded at baseline. The severity of paresis was calculated as a sum score of 16 lower extremity muscle groups, based on manual muscle testing. The size of at least 10 motor units was estimated from multichannel surface EMG recordings. Enlarged mean motor unit size was defined as >4 mVms.

The medical ethics committees of the hospitals involved approved the study. All subjects gave their written informed consent.

Randomisation, blinding, and treatment regimen
Randomisation of treatment allocation was done in blocks of four. All treatment allocations were concealed for the patients as well as the researchers. The data analyst remained blinded until after the primary outcome analyses.

A dose of 60 mg pyridostigmine four times a day was given for 14 weeks. The dose was gradually increased during the first six days from 4x10 mg to 4x60 mg, to reduce the chance of adverse effects. From the fourth day onwards, 1.025 mg atropine was added at each dose to mask the parasympathetic effects of pyridostigmine. The placebo treated subjects also received pyridostigmine during the first three days in the same incremental dose to improve blinding. Subsequently, the pyridostigmine was phased out in two days, and from day 6 onwards placebo pyridostigmine was given. From day 4 onwards this was combined with placebo atropine. Drug treatment was taken 1.5 to 2 hours before each study visit. Compliance was checked by counting the remaining pills.

Study design
Subjects were measured five times: two baseline visits, with a three week interval to check for learning effects, a visit in the fifth and the 14th week of treatment to evaluate acute and chronic effects, and a visit three weeks after cessation of treatment. For each subject, all visits were scheduled at the same time of day. The drug treatment started two weeks after the second baseline visit (range one to three).

Outcome measures
Primary outcome was the category “energy” in the Nottingham health profile (NHP). Unweighted sum scores ranged from 0 (no complaints) to 100 (answered yes to all questions).

Secondary outcomes included questionnaires and measurements of physical performance and muscle function.

Questionnaires
The following questionnaires were used:

- The fatigue severity scale (FSS), with a score ranging from 1 (no effect of fatigue on daily life) to 7 (severe, disabling fatigue).
- The subjective benefit of the treatment, with two questions: (1) “What, in your opinion, is the effect of the treatment?”, with answers ranging from 1: “very much worse”, to 7: “very much improved”; and (2) “Compared to the period before treatment, your fatigue complaints have …?”, with answers ranging from 1: “greatly increased”, to 7: “greatly decreased”. A score of 4 indicated no change.

Physical performance
Physical performance was assessed in the following ways:

- The duration of walking in the daily environment, measured with an ambulatory activity monitor. The sum of walking activities (that is, continuous walking for at least five seconds) in a 48 hour recording was expressed as the percentage of the total recording time. Walking duration was measured at baseline and in the last week of the drug treatment in 24 consecutively enrolled subjects (10 pyridostigmine, 14 placebo).

Muscle function
Muscle function was determined as follows:

- Maximum quadriceps strength on a chair dynamometer (Kinetic Communicator, Chattecx Corporation, Chattanooga Tennesse, USA). Subjects undertook three isometric maximum voluntary contractions (MVC) at an optimal knee angle with a two minute rest interval; the greatest contraction was included in the analysis.

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Sample size and statistical analysis
With a power of 90% and a significance level of 0.05, 50 subjects would be needed to show a one item improvement in the secondary outcome measures. The minimum clinical relevant improvement in the secondary outcome measures was set at 10%. The analyses were based on an intention to treat approach. Subgroup analyses were done for motor unit size (enlarged and normal), and for walking distance and quadriceps strength, for which subgroups were formed on the basis of the median baseline value. All tests were two sided, and statistical significance was set at p<0.05.
RESULTS
Sixty seven of the 101 subjects who were screened were included (fig 1). The two groups were comparable with respect to demographic and baseline characteristics (table 1).

Two subjects were excluded after treatment allocation because of thyroid dysfunction and anaemia. Two subjects withdrew from the study, one (pyridostigmine) after four weeks of treatment because of personal circumstances, and one (placebo) after six weeks of treatment because of dissatisfaction with the procedures. In general, the treatment was well tolerated. One subject (pyridostigmine) discontinued the drug because of severe diarrhoea, and was lost to follow up for personal reasons.

Compliance and blinding
Compliance was good. Fifty five of the 62 subjects who completed the study took at least 90% of their drug dose. Only two subjects (placebo) took less than 80% of their dose.

The blinding code was not broken during the trial, and the blinding was successful—68% of the subjects receiving pyridostigmine and 47% of the subjects receiving placebo guessed their actual treatment correctly (p = 0.37). The investigator guessed correctly for 39% of the pyridostigmine treated subjects and for 42% of the placebo treated subjects (p = 0.20).

Outcome
There was no significant difference in change on the primary outcome NHPF between the two groups during the treatment period (table 2). In the 14th week of treatment, a significant reduction of 36% was found in both groups. No difference in change on the FSS or in the subjective benefit of the treatment was found between the two groups; both improved significantly during the treatment period.

In the 14th week of treatment, the walking distance improved more in the pyridostigmine group than in the placebo group (by 7.2 m (6.0%); p = 0.003). No effect of pyridostigmine was found on maximum walking performance. Three weeks after the treatment period the pyridostigmine group improved significantly more than the placebo group on walking distance and maximum walking performance. No difference in change in the duration of walking was found between the two groups. Walking duration increased significantly in the pyridostigmine group.

There was no difference in change in quadriceps strength between the two groups. In the 14th week of treatment, significant improvements were found in both groups. In the

Figure 1 The number of subjects measured at the study visits during the trial and the compliance with the study drug in the two groups.
last week of treatment, 58% of the subjects in the pyridostigmine group improved on both quadriceps strength and walking distance, whereas 13% of the subjects in this group did not improve on either of these outcome measures (p<0.05, χ² test). In the placebo group, 32% improved on both outcome measures, whereas 19% did not (p = 1.00).

In 24 subjects (10 pyridostigmine, 14 placebo), MVA could be measured owing to inability to stimulate the quadriceps to exert at least 25% of the MVC (n = 21) or because of intolerance of the measurement (n = 3). In the fifth week of treatment and three weeks after the treatment period, 60% had improved significantly more in the pyridostigmine group than in the placebo group (table 2), probably caused by large variation in neuromuscular transmission defects between endplates, indicates that the reproducibility of jitter was poor. Thus jitter was not an appropriate measure to establish the effectiveness of the pyridostigmine dose.

Data on muscle fatigability were missing for seven subjects in both the pyridostigmine and the placebo groups owing to recording artefacts. Muscle fatigability did not change in either group.

Jitter values were missing for three subjects in the placebo group (intolerance in two, technical failure in one) in the last week of treatment. No difference in change in jitter was found between the two groups.

### Subgroup analyses

Motor unit size was missing in four subjects (three pyridostigmine, one placebo) owing to technical failures. Motor unit size was increased in 23 subjects (12 pyridostigmine, 11 placebo) and was normal in 35 subjects (16 pyridostigmine, 19 placebo). For the subjects with enlarged motor units, no difference in change between the two groups was found for any outcome measure. For the subjects with normal sized motor units, walking distance improved 2.9 s more (4.5%; p = 0.03) in the pyridostigmine group than in the placebo group. No differences in effects were found for subgroups based on walking distance or quadriceps strength.

### DISCUSSION

Our study provided no evidence of any benefit of pyridostigmine in reducing fatigue in patients with postpoliomyelitis syndrome with increased fatigue and neuromuscular transmission defects in a quadriceps muscle with new neuromuscular symptoms. The only significant difference in change between the two study groups in the 14th week of treatment was for walking distance, though the improvement of 6% was less than considered clinically relevant. The main question to be answered is whether pyridostigmine is indeed ineffective as a treatment for postpoliomyelitis syndrome, or whether the negative result reflects shortcomings of the study.

#### Was the dose of pyridostigmine adequate?

Taking into account the negative result of a randomised controlled trial with 180 mg a day, we increased the dose of pyridostigmine to 240 mg. To assess whether this dose was pharmacologically effective, changes in neuromuscular transmission defects were monitored (S-SFEMG). The fact that no significant improvement in neuromuscular transmission was found in the pyridostigmine group might suggest that the dose of 240 mg was not adequate. However, the large standard deviation of the change in jitter found in the placebo group (table 2), probably caused by large variation in neuromuscular transmission defects between endplates, indicates that the reproducibility of jitter was poor. Thus jitter was not an appropriate measure to establish the effectiveness of the pyridostigmine dose.

Nonetheless, plasma concentrations of pyridostigmine can vary greatly between individuals, and the dose may have been insufficient for an unknown number of subjects. This implies that individual adjustment may be required to obtain an effective dose.

#### Was the ability to detect an effect of pyridostigmine adequate?

The sample size of the study population was calculated with an expected standard deviation of 30 in the change in NHPₑ score. The NHPₑ scores which were obtained were in agreement with this assumption and confirmed an adequate power calculation. However, the NHPₑ showed a substantial ceiling effect at baseline, where 15 subjects (23%) had a score of 0. In addition, the NHPₑ scores in the placebo group decreased significantly during the treatment period. To demonstrate a beneficial effect of pyridostigmine, the scores in the pyridostigmine group would have to decrease by more than 33%, which was only found possible in 15 subjects.

Fatigue was also measured with the FSS, which has more response choices and showed no ceiling effect. As the FSS also failed to improve with pyridostigmine, the lack of effect on the NHPₑ cannot be attributed to an insufficient number of subjects. This implies that individual adjustment may be required to obtain an effective dose.

#### Does pyridostigmine have an effect on muscle function?

In this study, many comparisons were made and statistically tested. By chance, multiple testing can yield significant differences that do not reflect true differences and may produce misleading results. Some of the significant differences found—for instance, on maximum walking performance and MVA three weeks after treatment—may therefore be coincidental. However, if these differences had resulted from chance alone, they would have been equally distributed over the two treatment groups. The significant improvements in walking distance, the duration of walking, quadriceps strength, and MVA were all in favour of the pyridostigmine.

### Table 1

Baseline characteristics according to treatment group

<table>
<thead>
<tr>
<th>Characteristics/ outcome measures</th>
<th>Pyridostigmine (n = 33)</th>
<th>Placebo (n = 32)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51 (8)</td>
<td>52 (8)</td>
<td>0.61</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/23</td>
<td>13/19</td>
<td>0.38</td>
</tr>
<tr>
<td>Age at polio onset (years)</td>
<td>3.4 (4.3)</td>
<td>2.5 (2.5)</td>
<td>0.31</td>
</tr>
<tr>
<td>Duration of PPS symptoms (years)</td>
<td>10.0 (5.9)</td>
<td>10.7 (6.3)</td>
<td>0.64</td>
</tr>
<tr>
<td>Severity of areflexia of the legs (range 0–48)</td>
<td>24 (5)</td>
<td>22 (6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Mortar unit size (mV·ms⁻¹)</td>
<td>3.7 (2.4)*</td>
<td>3.9 (2.5)**</td>
<td>0.75</td>
</tr>
<tr>
<td>Shortened fatiguability questionnaire (range 4–28)</td>
<td>20 (6)</td>
<td>19 (5)</td>
<td>0.63</td>
</tr>
<tr>
<td>Nottingham health profile, category “Energy” (range 0–100)</td>
<td>47 (34)</td>
<td>47 (36)</td>
<td>0.95</td>
</tr>
<tr>
<td>Fatigue severity scale (range 1–7)</td>
<td>5.6 (0.8)</td>
<td>5.8 (1.0)</td>
<td>0.38</td>
</tr>
<tr>
<td>Two minute walking distance, comfortable speed (m)</td>
<td>122 (21)</td>
<td>117 (27)</td>
<td>0.37</td>
</tr>
<tr>
<td>Maximum walking performance, 75 m (s)</td>
<td>58 (14)</td>
<td>64 (22)**</td>
<td>0.22</td>
</tr>
<tr>
<td>Walking duration (percentage of total time)</td>
<td>6.5 (2.9)*</td>
<td>7.0 (2.7)**</td>
<td>0.70</td>
</tr>
<tr>
<td>Quadriceps strength (N·m)</td>
<td>90 (43)</td>
<td>82 (48)</td>
<td>0.51</td>
</tr>
<tr>
<td>Maximum voluntary activation (range 0–100)</td>
<td>70 (17)%</td>
<td>69 (22)%</td>
<td>0.94</td>
</tr>
<tr>
<td>Muscle fatiguability on surface EMG (MF₀–MF₂)</td>
<td>1.3 (2.2)*</td>
<td>2.3 (3.0)**</td>
<td>0.17</td>
</tr>
<tr>
<td>Neuromuscular transmission, jitter (µs)</td>
<td>40 (13)</td>
<td>40 (14)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

*Except for sex, values are presented as mean (SD). Differences between the two groups were tested by t tests (χ² for sex). n = 9; n = 12; n = 23; n = 28; n = 29; *n = 30; †n = 31.

PPS, postpoliomyelitis syndrome.
<table>
<thead>
<tr>
<th></th>
<th>Week 5 of treatment</th>
<th>Week 14 of treatment</th>
<th>Three weeks after end of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSM (n = 31)</td>
<td>Placebo (n = 31)</td>
<td>PSM (n = 31)</td>
</tr>
<tr>
<td><strong>NHP (range 0–100)</strong></td>
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<tr>
<td></td>
<td>−10.8 (35.9)</td>
<td>−10.8 (26.4)</td>
<td>0.0 (16.0 to −16.0)</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>p = 0.11</td>
<td>p = 0.03</td>
<td>p = 0.01</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>−26.4 to 0.0</td>
<td>0.0 to 16.0</td>
<td>−16.0 to 16.0</td>
</tr>
<tr>
<td><strong>QSS (range 1–7)</strong></td>
<td>−0.2 (0.7)</td>
<td>−0.4 (0.5)</td>
<td>0.1 (−0.2 to 0.4)</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>p = 0.07</td>
<td>p &lt; 0.01</td>
<td>p = 0.01</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
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</tr>
<tr>
<td></td>
<td>−3.5 to 1.1</td>
<td>−2.9 to 0.0</td>
<td>−0.5 to 0.5</td>
</tr>
<tr>
<td>Subjective benefit of treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Question 1</strong></td>
<td>0.5 (0.7)</td>
<td>0.5 (0.8)</td>
<td>−0.1 (−0.5 to 0.3)</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.001</td>
<td>p = 0.01</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
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</tr>
<tr>
<td></td>
<td>−1.0 to 1.5</td>
<td>−0.9 to 0.6</td>
<td>−0.6 to 0.6</td>
</tr>
<tr>
<td>Two minute walking distance (m)</td>
<td>5.8 (5.9)</td>
<td>2.8 (−1.4 to 7.0)</td>
<td>10.2 (9.4)</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
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<tr>
<td><strong>95% CI</strong></td>
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<tr>
<td></td>
<td>−11.1 to 11.6</td>
<td>−4.6 to 0.0</td>
<td>−7.2 to 2.6</td>
</tr>
<tr>
<td>Max walking performance, 75 m (s)</td>
<td>0.5 (5.8)</td>
<td>−1.5 (−4.0 to 0.9)</td>
<td>−1.6 (4.4)</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>p = 0.09</td>
<td>p = 0.76</td>
<td>p = 0.06</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>−2.9 to 1.9</td>
<td>−3.7 to 0.3</td>
<td>−2.7 to 1.9</td>
</tr>
<tr>
<td>Duration of walking (% of total time)</td>
<td>1.5 (1.3)</td>
<td>1.0 (1.7) *</td>
<td>1.0 (1.7) *</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.001</td>
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<td><strong>95% CI</strong></td>
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<td></td>
<td>−3.0 to 1.1</td>
<td>−2.2 to 1.7</td>
<td>−1.8 to 1.7</td>
</tr>
<tr>
<td>Quadriceps strength (Nm)</td>
<td>6.7 (13.7)</td>
<td>5.0 (13.9)</td>
<td>12.7 (21.4)</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>p = 0.01</td>
<td>p = 0.006</td>
<td>p = 0.01</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>−11.5 to 4.9</td>
<td>−6.9 to 0.0</td>
<td>−24.0 to 12.7</td>
</tr>
<tr>
<td>Max voluntary activation (range 0–100)</td>
<td>6.5 (14.3)†</td>
<td>−4.7 (11.3)†</td>
<td>11.1 (30.0 to 19.3)</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>p = 0.04</td>
<td>p = 0.09</td>
<td>p = 0.01</td>
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<tr>
<td><strong>95% CI</strong></td>
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</tr>
<tr>
<td></td>
<td>−14.3 to 4.2</td>
<td>−11.3 to 4.6</td>
<td>−33.3 to 22.1</td>
</tr>
<tr>
<td>Muscle fatigability (MF0.5%·MF25–35%)</td>
<td>0.1 (2.9)**</td>
<td>−0.0 (3.5)†</td>
<td>0.2 (−1.6 to 1.9)</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>p = 0.82</td>
<td>p = 0.98</td>
<td>p = 0.18</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
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</tr>
<tr>
<td></td>
<td>−11.1 to 11.3</td>
<td>−2.9 to 0.0</td>
<td>−2.1 to 1.6</td>
</tr>
<tr>
<td>NMT, jitter (μs)</td>
<td>−5.6 (16.0)</td>
<td>−2.8 (21.1)†</td>
<td>−2.8 (−12.6 to 7.9)</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>p = 0.06</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
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<tr>
<td><strong>95% CI</strong></td>
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<tr>
<td></td>
<td>−11.6 to 5.6</td>
<td>−10.1 to 6.9</td>
<td>−12.0 to 6.9</td>
</tr>
</tbody>
</table>

Change is calculated as the scores at or after intervention minus the scores at baseline and is presented as mean (SD). The difference in change between groups (Δ) is calculated from the change in the pyridostigmine group minus the change in the placebo group and is presented as mean difference (95% confidence interval) and the p value of the t test.

* n = 9; t n = 12; § n = 19; * n = 20; † n = 23; ** n = 26; †† n = 28; ††† n = 29; $ n = 30.

CI, confidence interval; FSS, fatigue severity scale; Max, maximum; MF, median frequency; NHP, Nottingham health profile, category “energy”; NMT, neuromuscular transmission; PSM, pyridostigmine.
group. These findings suggest that pyridostigmine does improve muscle function to some extent. This is also supported by the significant association between the improvement in walking performance and the improvement in quadriceps strength, which was found in the pyridostigmine group but not in the placebo group.

It was expected that pyridostigmine would slow down muscle fatigueability. However, no changes were found on the surface EMG during the treatment period in either of the two groups. The protocol used, with a sustained contraction at 40% of MVC (as obtained at baseline), did not induce high levels of fatigue, as was shown by the small decline in MF at baseline. This left little opportunity for improvement, and a relatively higher level of effort might have been more appropriate.

**Do subjects with normal sized motor units benefit more from pyridostigmine?**

It was hypothesised in advance that subjects with enlarged motor units would benefit most from pyridostigmine.\(^9\)\(^15\) Contrary to this expectation, subjects with normal sized motor units improved in walking performance, while those with enlarged motor units did not. Although this unexpected subgroup effect must be interpreted with caution, it should be realised that all quadriceps muscles were symptomatic, and all showed abnormal neuromuscular transmission. An explanation might be that the normal sized motor units were, in fact, enlarged motor units that had become reduced in size over time owing to the distal degeneration of axonal branches.\(^12\)\(^38\)\(^39\)

**Conclusions**

The result of this trial was negative, as pyridostigmine did not reduce fatigue in a selected group of subjects with postpolio myelitis syndrome who were most likely to benefit from this treatment. On the other hand, the significant effect of pyridostigmine on walking distance—together with some effects on walking duration, quadriceps strength, and maximum voluntary activation—suggest that pyridostigmine may improve muscle function. The effect of pyridostigmine might be related to the size of the motor units with neuromuscular transmission defects. In subjects with normal sized motor units, the effect size might be of relevance. However, a confirmatory study is needed as this finding resulted from a subgroup analysis that was not prespecified. Because no effect was found on perceived fatigue, future studies should concentrate on the effects of individually adjusted doses of pyridostigmine on physical performance in subjects with postpolio myelitis syndrome.

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