

# Fatigue in progressive multiple sclerosis: results of a randomized, double-blind, placebo-controlled, crossover trial of oral 4-aminopyridine.

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## Abstract

Previous studies suggest that aminopyridine may play a role in the symptomatic treatment of fatigue in multiple sclerosis. Although the mechanism underlying the beneficial effect on fatigue remains unclear, it has been proposed that aminopyridines may help to improve conduction in demyelinated central pathways, implicating both axonal and synaptic mechanisms. The objective of the present study is to determine whether 4-AP decreases daily-living fatigue in progressive multiple sclerosis. The effect of 4-AP on other neurophysiological and neuropsychological parameters was also considered. A 'double-blind', randomized, 'placebo-controlled', crossover trial was conducted on 54 patients with progressive multiple sclerosis. All patients received treatment with placebo and 32 mg per day of 4-AP, each for 6 months. The main outcome measure was the Fatigue Severity Scale. Secondary measures were EDSS, cognitive functions and neurophysiological parameters. Forty-nine patients (91%) completed the study. Changes in fatigue scores, EDSS and cognitive functions were not significantly different between 4-AP and placebo. However, when patients treated with 4-AP were divided into two groups according to the serum level of 4-AP, a significant effect on fatigue compared with placebo was observed in the 'high level' (>30 ng/ml) group ( $P=0.05$ ). Synchronization of motor evoked potentials improved during 4-AP with respect to placebo ( $P=0.019$ ) and this correlated positively with fatigue reduction ( $P=0.010$ ). No relevant side effects were observed.

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