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File: ■ Rhodiola (*Rhodiola rosea*, Crassulaceae)
■ Chronic Fatigue

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RE: Exploratory Trial Suggests Rhodiola May Benefit Prolonged or Chronic Fatigue

Lekomtseva Y, Zhukova I, Wacker A. *Rhodiola rosea* in subjects with prolonged or chronic fatigue symptoms: results of an open-label clinical trial. *Complement Med Res*. February 2017;24(1):46-52.

Fatigue is defined as feeling tired or lacking energy, emotional stability, or motivation, and/or having difficulty in concentration and memory. Prolonged fatigue is defined as fatigue lasting 1 to 6 months, while chronic fatigue lasts for > 6 months. There is no standard treatment for fatigue of unknown etiology. Treatment often involves exercise or cognitive behavioral therapy. Stress may precipitate the onset of prolonged/chronic fatigue. Adaptogens, which increase resistance to stress, may treat prolonged or chronic fatigue. The objective of this open-label, single-arm, multicenter study was to evaluate the effect, safety, and tolerability of the adaptogen rhodiola (*Rhodiola rosea*, Crassulaceae) root extract on patients with prolonged or chronic fatigue.

Patients with prolonged or chronic fatigue symptoms were recruited from neurology departments of 5 hospitals in the Ukraine. Study dates were December 2011 to May 2012. Included patients had (1) fatigue symptoms lasting for at least 2 months that were not the result of a diagnosed illness or exertion, not adequately relieved by rest, and interfering with major life activities; (2) a score of ≥ 5 on the Numeric Analog Scales (NASs) for "postexertional malaise lasting more than 24 hours," "substantial impairment in short-time memory and concentration," and "unrefreshing sleep"; (3) Multidimensional Fatigue Inventory 20 (MFI-20) score ≥ 7 for the subscales "general fatigue," "physical fatigue," and "mental fatigue"; and (4) the ability to respond to interview questions and complete self-assessment scales without assistance of an interpreter.

Excluded patients (1) participated in another drug trial; (2) were currently hospitalized; (3) had Beck Depression Inventory II (BDI-II) item 9 ≥ 1; (4) had substance abuse or dependence within the last 5 years; (5) had Axis I disorders according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, within 1 year; (6) had non-medical psychiatric treatment within 4 weeks; (7) could not discontinue or might need any psychotropic drugs; (8) had clinically significant abnormal electrocardiography (ECG) or laboratory values; (9) had cardiovascular disease, respiratory disease,

metabolic disorders, progressive disease, cerebrovascular/neurologic disease, any infection, or gastrointestinal condition that may affect absorption of orally administered drugs; (10) were pregnant or lactating, or, if female and premenopausal, would not agree to use "sufficient" contraception; or (11) had known hypersensitivity to rhodiola.

Patients received 400 mg/day dry ethanolic rhodiola extract (WS® 1375; Rosalin®; Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe, Germany) for 8 weeks; one 200-mg tablet was taken before breakfast and 1 before lunch. The following assessments were conducted at baseline and at 1, 4, and 8 weeks: MFI-20 to measure fatigue; NASs to measure chronic fatigue symptoms; Numbers Connecting Test (NCT) to assess the speed of executive function; Sheehan Disability Scale (SDS) to assess how panic, anxiety, depression, or phobia disrupt the patient's work, social life, and family life; and the Clinical Global Impressions (CGI) scale with the items "change from baseline," "therapeutic efficacy," and "tolerability" assessed in an interview. At 4 and 8 weeks, the following 3 additional assessments were conducted: the Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality and disturbances; Recent Perceived Stress Questionnaire (PSQ-R) to assess subjective stress; and the BDI-II to assess depression. Safety and tolerability were assessed via physical examinations, laboratory data, and vital signs measurements between baseline and week 8, and assessment of adverse events (AEs).

Of 101 patients enrolled, 1 was removed early for violation of exclusion criteria, while 100 (mean age, 37.8 years [67% female]) completed the study. Treatment compliance was good. The MFI-20 assessment had significant improvement on all subscales ($P < 0.0001$), with the greatest change occurring at the end of week 1, but improvement continuing to week 8. The greatest change occurred on the subscale of "general fatigue." NASs had significant improvement between baseline and subsequent visits ($P < 0.0001$). The total SDS score and measures for "impairment at work," "impairment in social life," and "impairment in family life" improved significantly at week 8 compared with baseline ($P < 0.0001$). The NCT, PSQI, BDI-II, and PSQ-R significantly improved between baseline and week 8 ($P < 0.0001$ for all). The baseline PSQ-R score indicated that the patients had significant preexisting stress; they experienced a clinically relevant 41.8% mean reduction in total stress. Among the PSQ-R subscores, "fatigue" decreased by 38.8% at week 8. On the CGI, 83.0% of patients were reported to be "very much" or "much" improved at week 8. Approximately 41% of patients had a total of 44 AEs, of which 81.8% were mild, with 72.7% of AEs assessed as "not related" to the treatment and causality for the remainder unknown but generally considered "unlikely." None of the patients discontinued the study due to an AE. The 3 most common categories were gastrointestinal symptoms, nervous symptoms, and "infections and infestations." There were no clinically relevant changes in laboratory parameters, 12-lead ECG, or vital signs.

Nearly all outcome measures significantly improved over time and continued to decline to week 8, and the treatment was safe and well tolerated. Taken together, the authors conclude that the significant improvement in measures not only of core fatigue symptoms but a broad variety of symptoms and consequences of fatigue suggests a good potential for rhodiola to improve quality of life in chronic fatigue. An important limitation of this study is that it was open-label; thus, a placebo effect cannot be ruled out, nor can simple reversion to the mean in patients whose symptoms were not of long standing. The authors acknowledge that the study is exploratory.

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—Heather S. Oliff, PhD

Referenced article can be accessed at https://www.karger.com/Article/FullText/457918.