

## **Iron supplementation for fatigue in non-anemic women. A double-blind randomized placebo controlled trial**

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**Objective:** To document a subjective response to iron therapy in non-anemic pre-menopausal women complaining of fatigue.

**Methods:** The design is a double-blind, placebo-controlled prospective study. Subjects were recruited in an academic primary care center and in 11 general practices. The inclusion criteria were women between 18 and 55 years old, complaining of unexplained fatigue after ruling out somatic disorders. Patients with the chronic fatigue syndrome or evidence of depression were excluded; 131 participants were randomly assigned either to oral ferrous sulfate (80 mg once daily) or placebo for 4 weeks. After one month, women (n=69) with a low serum ferritin concentration (below or equal 20 ug/l) received iron for two additional months in an open design. The follow-up for all patients was 3 months. The effect of iron treatment was assessed by questionnaires (a 10-point Likert scale of fatigue and a selfreport visual analogic scales of fatigue, depression and anxiety). Adherence to treatment was verified by an electronic device recording file date and time of every opening of the pill container. Intention-to-treat and per-protocol analysis were done.

**Results:** Of the 144 enrolled women (75 were randomized in the iron group and 69 in the placebo group), 131(91%) completed the study (69 in file iron group and 62 in file placebo group). Mean age, serum ferritin concentration, level of fatigue, depression and anxiety did not differ significantly at baseline. Compliance and drop-out rates were similar in both groups. Univariate and multiplelinear regression analysis showed that the level of fatigue after one month was significantly improved for the group who received iron in comparison with the placebo group ( $p<0.002$ ). This improvement was independent of the depression or anxiety scores. Interestingly, among the women in file iron group, the best predictor of response (in a regression analysis) was the amount of iron consumed and not the serum ferritin at baseline ( $p=0.007$ ). After the first month, the patients who received iron because of a low level of ferritin were greatly improved at 3 months in comparison with no treatment at all ( $p=0.0005$ ).

**Conclusions:** Iron supplementation even in file absence of anemia may be beneficial to women complaining of unexplained fatigue.