

Research article

# Cortisol and hypothalamic–pituitary–gonadal axis hormones in follicular-phase women with fibromyalgia and chronic fatigue syndrome and effect of depressive symptoms on these hormones

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Received: 20 Aug 2003 Revisions requested: 26 Sep 2003 Revisions received: 6 Feb 2004 Accepted: 19 Feb 2004 Published: 15 Mar 2004

*Arthritis Res Ther* 2004, **6**:R232-R238 (DOI 10.1186/ar1163)

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## Abstract

We investigated abnormalities of the hypothalamic–pituitary–gonadal axis and cortisol concentrations in women with fibromyalgia and chronic fatigue syndrome (CFS) who were in the follicular phase of their menstrual cycle, and whether their scores for depressive symptoms were related to levels of these hormones. A total of 176 subjects participated – 46 healthy volunteers, 68 patients with fibromyalgia, and 62 patients with CFS. We examined concentrations of follicle-stimulating hormone, luteinizing hormone (LH), estradiol, progesterone, prolactin, and cortisol. Depressive symptoms were assessed using the Beck Depression Inventory (BDI). Cortisol levels were significantly lower in patients with fibromyalgia or CFS than in healthy controls ( $P < 0.05$ ); there were no significant differences in other hormone levels between the three groups.

Fibromyalgia patients with high BDI scores had significantly lower cortisol levels than controls ( $P < 0.05$ ), and so did CFS patients, regardless of their BDI scores ( $P < 0.05$ ). Among patients without depressive symptoms, cortisol levels were lower in CFS than in fibromyalgia ( $P < 0.05$ ). Our study suggests that in spite of low morning cortisol concentrations, the only abnormalities in hypothalamic–pituitary–gonadal axis hormones among follicular-phase women with fibromyalgia or CFS are those of LH levels in fibromyalgia patients with a low BDI score. Depression may lower cortisol and LH levels, or, alternatively, low morning cortisol may be a biological factor that contributes to depressive symptoms in fibromyalgia. These parameters therefore must be taken into account in future investigations.

**Keywords:** chronic fatigue syndrome, cortisol, depression, fibromyalgia, hypothalamic–pituitary–gonadal axis

## Introduction

Because fibromyalgia syndrome and chronic fatigue syndrome (CFS) share symptoms, it may be asked whether fibromyalgia and CFS are two entities or only two syndromes of a spectrum of similar disorders of common etiology and pathogenesis. Fibromyalgia and CFS are clinically overlapping, stress-related syndromes that primarily affect women [1,2]. Fibromyalgia is characterized by widespread chronic pain affecting the musculoskeletal system, with defined tender points apparent on examination [3]. It is also associated with sleep disturbance and fatigue, suggesting overlap with CFS. In addition, patients with CFS often complain of

musculoskeletal discomfort accompanied by tender points. Neuroendocrine abnormalities have been observed in both disorders, including dysregulation of the hypothalamic–pituitary–adrenal (HPA) and hypothalamic–pituitary–gonadal (HPG) axes [4–6].

Endocrine regulation is considerably impaired in both conditions, with many hormonal mechanisms altered. Therefore, neuromediator and hormonal abnormalities may play an important role in the pathogenesis of fibromyalgia and CFS [7]. An increasing amount of literature dealing with endocrine and neuroendocrine data in fibromyalgia and CFS has been published in the past several years.

BDI = Beck Depression Inventory; CFS = chronic fatigue syndrome; FSH = follicle-stimulating hormone; HPA = hypothalamic–pituitary–adrenal; HPG = hypothalamic–pituitary–gonadal; LH = luteinizing hormone.

The central stress axis, the HPA axis, seems to play an important role in fibromyalgia and CFS. Early investigations postulated hypofunction of the HPA axis in these conditions, based on the finding of low urinary free cortisol, and suggested the hypothesis of a common pathogenesis [8].

Both fibromyalgia and CFS occur more commonly in women, and there is an increasing incidence of fibromyalgia perimenopausally and postmenopausally. This suggests that alterations in reproductive hormone levels may be involved in the etiopathology of fibromyalgia and CFS. Additionally, there have been reports that both conditions may be due to estrogen deficiency and reflect underactivity of the HPG axis [9,10]. Stress has been shown to inhibit gonadotropin-releasing hormone and the pulsatile secretion of luteinizing hormone. Infusion of corticotropin-releasing hormone into the cerebral ventricles leads to inhibition of LH secretion in primates [11]. Perturbations of HPA axis function have been described in fibromyalgia and CFS [4,6].

It is increasingly clear that the HPA axis is hyperactive in fibromyalgia but is typically hypoactive in CFS. One reason for confusion in endocrinologic research on fibromyalgia and CFS is the imprecise definition of the two conditions, their frequent overlap, and confounding psychiatric conditions that may also affect neuroendocrine axes [7]. The phase of the patient's menstrual cycle may also affect findings. For all these reasons, findings are strongly dependent on the patients selected for investigation.

There is no explanation for the higher frequency of fibromyalgia in women, which suggests that sex hormones may have a role in the expression of the disease. Although the majority of fibromyalgia patients are female, only a few investigations have paid attention to the changes of sex hormones in fibromyalgia [12–14]. Riedel and colleagues [12] investigated female fibromyalgia patients and controls who were all in the follicular phase of their menstrual cycle. They found that fibromyalgia patients had significantly lower estrogen levels despite elevated FSH levels. Korszun and colleagues [13] and Akkus and colleagues [14] found no differences from controls in values of FSH and LH in patients with fibromyalgia.

Interaction between the HPA and HPG axes in stress-induced amenorrhea suggests that there may be perturbations of these axes in fibromyalgia and CFS that contribute to these stress-related diseases. It is important to detect the role of HPA and HPG axes in the pathogenesis of fibromyalgia and CFS, to define new treatment strategies for both. In previous studies of the conditions, the hormone levels of the HPA and HPG axes were not evaluated in the same patients. This is the first

study of both the HPG axis and cortisol, which is the most important hormone of the HPA axis, in follicular-phase women with fibromyalgia and CFS, and the first to evaluate the relation between depressive symptoms and these hormones in the same patients.

We aimed to investigate abnormalities of the HPG axis and cortisol concentrations in follicular-phase women with fibromyalgia and CFS, and to find out whether the depressive symptom scores had any relation to these hormones.

## Materials and methods

Initially, the 203 subjects studied comprised 46 healthy volunteers, 68 patients with fibromyalgia only, 62 with CFS only, and 27 with fibromyalgia and comorbid CFS; patients were recruited from the Department of Physical Medicine and Rehabilitation, University Hospital of Dicle, Diyarbakır, Turkey. The 27 patients who met the criteria for both CFS and fibromyalgia were excluded and the study was therefore completed with 176 subjects. The diagnosis of fibromyalgia was based on the 1990 American College of Rheumatology criteria [15] and CFS was diagnosed according to the International CFS Definition Criteria [16].

The Human Studies Research Committee of the University of Dicle, Diyarbakır, approved all procedures, and written informed consent was obtained from each subject prior to inclusion in the study. Patients who agreed to enroll in the trial were examined, and demographic, functional, and clinical characteristics were documented. All subjects had a regular menstrual cycle and were fertile.

All patients underwent medical screening that included physical examination and relevant investigations, including at least urinalysis; full blood count; measurements of urea, electrolytes, and erythrocyte sedimentation rate; and tests of thyroid and liver function. All patients and controls were evaluated in a structured psychiatric interview to exclude any additional psychiatric disorder prior to inclusion in the study. Included subjects had to be free of comorbid psychiatric disorders as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition [17]. Depressive symptoms were scored using the Beck Depression Inventory (BDI) in all patients and controls. Both patients with CFS and fibromyalgia were divided into two groups for high or low BDI score according to whether the BDI score was  $\geq 17$  or  $< 17$ , respectively. They were free of all medication except stable doses of thyroid hormone replacement in individuals with treated hypothyroidism. All prescription medications, included psychoactive and nonprescription medications, vitamins, and herbal remedies were tapered and then stopped at least 2 weeks before the study [5,18]. None of the patients or controls had frank hypocortisolism on endocrine assessment. Anyone with a current psychiatric

history or a past history of depression was excluded from the study. No patients or controls had received any oral or intra-articular corticosteroid therapy during the 3 months preceding the study. All patients and controls were experiencing normal menstrual cycles and were not taking any contraceptive pill or any other drugs affecting the metabolism of sex hormones or of cortisol. Anyone with abnormal laboratory studies or a current medical problem other than fibromyalgia or CFS was excluded. The other exclusion criteria were: active, unresolved, or suspected disease likely to cause fatigue; alcohol or other substance abuse within 2 years prior to onset of the chronic fatigue and any time afterward; and a body mass index  $\geq 45$ .

Blood samples were collected in the morning (08.30–10.30 h) after an all-night fast, and plasma was separated immediately by centrifugation; then sera obtained were stored at  $-20^{\circ}\text{C}$  until hormonal assay. All hormone values were assayed using Electro Chemiluminescence Immunoassay (ECLIA) (1010/1020 Elecsys Systems Immunoassay; Roche Diagnostics, Mannheim, Germany) method. Serum concentrations of follicle-stimulating hormone (FSH) (normal values 3.3–11.3 IU/l for the follicular phase and 1.8–8.2 IU/l for the luteal phase), luteinizing hormone (LH) (normal values 2.4–12.6 IU/l for the follicular phase and 1.0–11.4 IU/l for the luteal phase), estradiol (normal values 24.5–195 pg/ml for the follicular phase and 40–261 pg/ml for luteal phase), progesterone (normal values 0–1.6 ng/ml for the follicular phase and 1.1–21 ng/ml for the luteal phase), prolactin (normal values 3.1–24.6 ng/ml) and cortisol (normal values 6.2–19.4  $\mu\text{g}/\text{dl}$ ) were evaluated in all patients and controls. Patients and controls were studied during the follicular phase of the menstrual cycle, that is, within 10 days after the onset of menstruation.

### Statistical analyses

Statistical significance was tested using one-way analysis of variance and a post hoc Bonferroni test for multiple group comparisons. All statistical tests were two-tailed;  $P < 0.05$  was taken as the level of statistical significance. Values are expressed as the mean  $\pm$  standard deviation.

### Results

Baseline characteristics of patients with fibromyalgia or CFS and of healthy controls are presented in Table 1.

BDI scores in both groups of patients were significantly higher than those of the control subjects ( $P < 0.05$ ), whereas there was no significant difference between the scores of the two groups of patients (Table 2). There were no significant differences in FSH, LH, estradiol, prolactin, or progesterone levels among all the groups, whereas cortisol levels were significantly lower in both groups of patients than in healthy controls ( $P < 0.05$ ). There was no

significant difference in cortisol levels between the two groups of patients (Table 2).

In this study, high BDI scores ( $\geq 17$ ), indicating depression, were detected in 53% and 66%, respectively, of patients with fibromyalgia and CFS (Table 3). Among the patients with fibromyalgia, cortisol levels were significantly lower in those with high BDI scores than in controls ( $P < 0.05$ ), but there was no significant difference between those low BDI scores and controls. There was no significant difference between fibromyalgia patients with and those without depressive symptoms. Cortisol levels in both groups of CFS patients were significantly lower than in controls ( $P < 0.05$ ). Additionally, cortisol levels in CFS patients without depressive symptoms were lower than those of fibromyalgia patients without depressive symptoms ( $P < 0.05$ ) (Table 3).

LH levels in fibromyalgia patients with low BDI scores were significantly higher than in those with high BDI scores and than in controls ( $P < 0.05$ ). There was no significant difference between LH levels in fibromyalgia patients with high BDI scores and controls. Additionally, among patients with low BDI scores, LH levels were significantly higher in patients with fibromyalgia than those with CFS ( $P < 0.05$ ) (Table 3).

### Discussion

In recent years, a novel and paradoxical phenomenon has emerged from neurobiological studies on the effects of stress. There is increasing evidence for a relatively decreased, rather than an increased, cortisol secretion in individuals who have been exposed to severe stress or suffer from stress-response-related disorders. The phenomenon of hypocortisolism has received growing attention in the field of stress research, inasmuch as it challenges or virtually reverses prevailing concepts on the neuroendocrinology of stress [19].

Both fibromyalgia and CFS are often viewed as being stress-response related, and abnormalities of the HPA axis have been found in both disorders. Stress is also known to disrupt the HPG axis, and the characteristic reproductive picture of 'stress'- or exercise-induced amenorrhea is that of infrequent LH pulses despite follicular-phase estradiol and progesterone levels [5]. Interestingly, abnormalities of the HPA axis reported in other stress-response-related disorders, such as hypothalamic amenorrhea and exercise-induced amenorrhea, involve increased baseline cortisol over 24 hours, whereas previous studies of fibromyalgia and CFS found low cortisol [6,20].

In our study, levels of reproductive HPG axis hormones during the follicular phase showed no significant differences in women with CFS or fibromyalgia from the values in controls. These findings are in agreement with those of

**Table 1****Baseline characteristics of patients and healthy control subjects**

Variable	Patients		Controls (N = 46)
	Fibromyalgia (N = 68)	Chronic fatigue syndrome (N = 62)	
Age (years)	31.43 ± 7.81	32.55 ± 6.61	31.54 ± 6.86
Disease duration (years)	3.96 ± 4.23	4.28 ± 4.12	–
FIQ score	59.23 ± 10.28	–	12.83 ± 7.21
Pain intensity (VAS)	5.03 ± 1.18	4.49 ± 1.83	0.47 ± 0.880
Tender point count	13.18 ± 1.79	6.49 ± 3.51	3.49 ± 2.81
Symptoms experienced [No. (%)]			
Morning stiffness	42 (62)	24 (39)	3 (7)
Muscle spasm	39 (57)	15 (24)	2 (4)
Fatigue	48 (71)	62 (100)	4 (9)
Skinfold tenderness	56 (82)	29 (47)	2 (4)
Sleep disturbance	54 (79)	27 (44)	2 (4)
Cigarette smoking	31 (46)	30 (48)	26 (57)
Menstrual cycle			
Age at menarche	12.91 ± 0.28	13.02 ± 0.25	13.14 ± 0.21
Cycle length (days)	13.14 ± 0.21	28.87 ± 0.19	29.07 ± 0.27
Days of menstrual flow	4.82 ± 0.36	4.97 ± 0.28	4.89 ± 0.32
Marital status [No. (%)]			
Married	45 (66)	39 (63)	28 (61)
Single	13 (20)	14 (23)	10 (23)
Divorced	7 (12)	6 (10)	4 (9)
Other	3 (2)	3 (4)	3 (7)
Highest educational level achieved [No. (%)]			
Elementary school	31 (46)	30 (48)	20 (44)
Secondary school	15 (22)	13 (21)	13 (28)
University/High school	22 (32)	19 (31)	13 (28)
Employment status [No. (%)]			
Unemployed	5 (7)	5 (8)	3 (7)
Employed	7 (10)	5 (8)	7 (15)
Retired	3 (4)	4 (6)	2 (4)
Homemaker	39 (58)	37 (60)	24 (52)
Student	11 (16)	8 (13)	7 (15)
Others	3 (5)	3 (5)	3 (7)

Values are means ± standard deviation, except where indicated as number and percentage of the group. FIQ, Fibromyalgia Impact Questionnaire; VAS: Visual Analog Scale; –, not applicable.

Korszun and colleagues [5], who reported data from nine premenopausal women with fibromyalgia and eight with CFS. They showed no significant differentiations of reproductive axis function in either group of patients with regard to estrogen and progesterone levels and to LH pulsatility during the follicular phase. However, our results are in contradiction to those of Studd and Panay [9], who

reported data from 28 premenopausal women with CFS. Of these, 25% showed low plasma estradiol concentrations. Those authors reported that CFS may represent a hypoestrogenic state and recommended the use of hormone replacement therapy for women with CFS. In addition, they claimed that 80% of patients improved after treatment with estradiol patches and cyclical progesta-

**Table 2**

**Serum hormones and scores on the Beck Depression Inventory (BDI) in patients and healthy control subjects**

Variable	Patients		Controls (N = 46)
	Fibromyalgia (N = 68)	Chronic fatigue syndrome (N = 62)	
BDI score	22.48 ± 12.53*	24.18 ± 12.67*	12.48 ± 5.83
LH	7.65 ± 6.45	6.63 ± 5.89	6.88 ± 4.69
FSH	5.92 ± 4.38	6.41 ± 4.35	6.69 ± 4.87
Progesterone	4.13 ± 5.76	3.69 ± 4.18	3.78 ± 3.97
Estradiol	113.24 ± 89.48	105.52 ± 101.12	94.15 ± 59.34
Prolactin	23.34 ± 17.12	24.19 ± 16.88	19.35 ± 10.45
Cortisol	10.14 ± 6.49*	10.38 ± 5.82*	13.52 ± 6.25

Values are means ± standard deviation. \*Significantly different from control value (P < 0.05). FSH, follicle-stimulating hormone; LH, luteinizing hormone.

**Table 3**

**Serum hormones in patients and control group according to score on the Beck Depression Inventory (BDI)<sup>a</sup>**

Variable	Patients with fibromyalgia		Patients with CFS		Healthy controls (N = 46)
	BDI < 17 (N = 32)	BDI ≥ 17 (N = 36)	BDI < 17 (N = 21)	BDI ≥ 17 (N = 41)	
Age (years)	31.86 ± 7.29	30.65 ± 7.65	31.98 ± 6.57	32.76 ± 7.18	31.54 ± 6.86
LH	11.65 ± 10.42* & #	6.43 ± 4.28	6.21 ± 7.26	6.71 ± 5.87	6.88 ± 4.69
FSH	7.13 ± 3.21	6.25 ± 2.84	5.87 ± 3.69	6.81 ± 4.43	6.69 ± 4.87
Progesterone	4.19 ± 4.56	4.73 ± 5.56	4.18 ± 4.65	3.72 ± 5.27	3.78 ± 3.97
Estradiol	113.48 ± 69.45	121.42 ± 90.26	98.39 ± 87.11	107.23 ± 91.57	94.15 ± 59.34
Prolactin	26.08 ± 32.19	21.03 ± 11.32	23.41 ± 28.49	20.87 ± 27.36	19.35 ± 10.45
Cortisol	11.94 ± 6.56#	10.11 ± 5.67*	8.96 ± 4.28*	10.52 ± 5.45*	13.52 ± 6.25

Values are means ± standard deviation. <sup>a</sup>A BDI score of ≥17 was considered to indicate depression. \*Significantly different from control (P < 0.05); & significantly different from fibromyalgia group with BDI ≥ 17 (P < 0.05); #significantly different from CFS group with BDI < 17 (P < 0.05). CFS, chronic fatigue syndrome; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

gens. A similar suggestion as to the effect of HRT has been made for women with fibromyalgia by Waxman and Zatskis [10]. The authors reported estrogen deficit as a prominent promoting factor in the majority of patients with fibromyalgia and recommended estrogen therapy for treatment of fibromyalgia. Further clinical and experimental studies are required to determine the role of sex hormones in the pathogenesis of this condition.

In our study, morning cortisol levels were lower in women with CFS than in healthy controls. Some studies of the HPA axis in CFS show a mild hypocortisolism of central origin, in contrast to hypercortisolism of major depression [21,22]. In an early study of the HPA axis in patients with CFS, Demitract and colleagues [6] reported low 24-hour

urine free cortisol compared with that of control subjects. Baseline evening plasma corticotropin levels were elevated and cortisol levels were depressed. Significantly lower baseline cortisol levels were reported in an earlier study [23]. However, most further studies have failed to replicate those findings. Differences in methodology, and sample characteristics, may explain the variety of results.

Previous studies suggested the existence of perturbation of the HPA axis in fibromyalgia [24,25], and a hyper-reactive response of adrenocorticotrophic hormone and GH to various stimuli was detected, whereas in the cortisol response, a decrease occurred [26–28]. Crofford [26] reported elevated serum levels of 24-hour free cortisol, resulting in a loss of normal diurnal cortisol

fluctuation, and with stimulation a brisk but lesser increase in cortisol level in fibromyalgia. An earlier study by Griep and colleagues [24] had found that neither basal levels nor stimulated levels of cortisol differed between groups. In a later study by the same group, mild hypocortisolemia was observed [29]. Again, differences in methodology, and sample characteristics, may explain the differences in results.

It is known that most patients with fibromyalgia and CFS also have depressive symptoms, and depressive patients suffering from pain are not uncommon. Some investigators have therefore suggested a possible connection between fibromyalgia, CFS, and depression. The first pointer to such a connection is that most patients with fibromyalgia and CFS exhibit depressive symptoms such as fatigue, sleep disturbances, and anxiety [30]. Second, phenomenological similarities exist between chronic pain syndrome – which has been claimed to be related to depression – and fibromyalgia [31]. Finally, an increased prevalence of depression has been found in patients with fibromyalgia, and bipolar illness has been diagnosed more frequently in close relatives of such patients [32]. Similarities in patients with fibromyalgia and depression [33] raise the possibility of a neuroendocrine relationship between these two disorders. It is unclear whether the depression develops as a reaction to the chronic pain or represents an independent disease within the fibromyalgia [34].

In our study, high BDI scores ( $\geq 17$ ) were detected in 53% and 66%, respectively, of patients with fibromyalgia and CFS. When compared according to score for depressive symptoms, cortisol levels were significantly lower in fibromyalgia patients with high BDI scores than in controls, but not in those with low BDI scores. Cortisol levels in CFS patients with and those without depressive symptoms were significantly lower than in controls, whereas there was no significant difference between fibromyalgia patients with and those without depressive symptoms. In patients without depressive symptoms, cortisol levels were lower in CFS than in fibromyalgia. Comorbid depressive illness is one important confounder present in approximately 50% of CFS patients [35]. High circulating cortisol is a well-replicated finding in major depression [36], and so presence of depression makes the cortisol findings more difficult to interpret. Of the 10 subjects studied by Wood and colleagues [37], 5 had high BDI scores. This may explain their finding of significantly raised baseline cortisol in their sample of CFS patients. Scott and Dinan [22] reported a finding of low urine free cortisol in patients with CFS compared with healthy controls. In addition, there was no difference in this constituent between depressed and nondepressed patients with CFS. In another study [38], the same group reported blunted corticotropin and cortisol in response to administration of ovine corticotropin-releasing hormone, without differences in basal levels.

In our study we found that the morning cortisol levels in the fibromyalgia patients with high BDI scores were significantly lower than those with low BDI scores. This is in contradiction to the hypercortisolism of classical major depression. In recent years, however, it has become increasingly apparent that depression is a heterogeneous condition, from both a psychological and a physiological perspective [39]. Moreover, decreased activity of the HPA axis was reported in some stress-related states such as CFS and atypical and seasonal depression [40]. Forms of depressive illness dominated by reduced energy, a reactive mood, and a reversal of the typical pattern of vegetative features seen in classical depression have been described [39]. There may be overlap between symptoms of fibromyalgia and those depressive subtypes or reactive forms of depression in fibromyalgia. This condition may explain the low cortisol levels in patients with fibromyalgia in this study. It may also explain both low morning cortisol in patients with CFS and the lack of abnormalities of hormones of the HPG axis in this study.

This is the first study comparing levels both of hormones of the HPG axis and of cortisol, which is the most important hormone of the HPA axis, in follicular-phase women with fibromyalgia and CFS and evaluating relations between scores for depressive symptoms and the HPG and HPA axes in these patients. Thus, comparison of CFS with fibromyalgia highlights both similarities and differences in neuroendocrinology. It may be that the differences reflect distinct pathophysiologies for the two syndromes. However, the similarities, both in reduced HPA activation, symptomatology, and abrupt stress-related onset, suggest otherwise.

Cortisol levels peak in early morning and need to be collected before patients rise in the morning; and determining single levels of hormones that are secreted in a pulsatile fashion may not be representative of normal functioning. But one should keep in mind that basal hormone levels alone do not reflect activity of the HPA and HPG axes. Sometimes only dynamic (stimulation) tests find differences in the activity of HPA and HPG axes in fibromyalgia. We did not carry out early-morning and repeated measures of these hormones because of the large number of subjects in our study. This point is a limitation of our study.

## Conclusion

Our study in follicular-phase women with fibromyalgia and CFS suggests that in these patients, despite low morning cortisol concentrations, the only abnormality in hormones of the HPG axis is high LH levels in fibromyalgia patients with low BDI scores. The score for depressive symptoms may have some relation to cortisol and LH levels, or low cortisol levels may be a biological factor that contributes to depressive symptoms in fibromyalgia. These parameters

therefore must be taken into account in future investigations. These results suggest that hormones of both the HPA and the HPG axis should be evaluated for an understanding of the pathophysiology of fibromyalgia and CFS and when considering approaches to treatment. Larger clinical studies and follow-up surveys are needed to clarify these matters.

### Competing interests

None declared.

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