Abnormal prolactin response in ME/CFS

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Introduction

Abnormal prolactin response in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a consistently replicated finding, but the implications of this finding have only been minimally explored. Further research into this phenomenon could potentially illuminate whether hormonal, neural, or other pathways are involved in the pathophysiology of ME/CFS.

Prolactin

Prolactin is a protein produced within several tissues in the human body, but its main site of synthesis is the anterior pituitary gland. This hormone is best known for its essential role in the development of mammary tissue and its ability to stimulate lactation. Additionally, prolactin exerts numerous other effects, which include the promotion of parental behavior, enhancement of immunity, modulation of lipid and glucose metabolism, and inhibition of the reproductive cycle during lactation. Suckling is the most potent natural stimulant of prolactin secretion, however stress, sounds, and circadian light patterns also affect the release of prolactin (1,2).

Unlike most hormones of the pituitary gland, prolactin is primarily regulated through inhibition instead of stimulation, whereby pituitary prolactin-secreting cells (lactotrophs) naturally secrete prolactin when hypothalamic influence is blocked. The main hormone involved in inhibiting prolactin is dopamine, which is released by neurons of the arcuate nucleus and periventricular nucleus of the hypothalamus, and which travels through the long or short portal veins to reach the lactotrophs. However, several other hormones appear to also have the ability to directly stimulate prolactin release by lactotrophs, and these include, but are not limited to, thyrotropin-releasing hormone (TRH), vasopressin, oxytocin, and vasoactive intestinal peptide (VIP) (2).

Neuroendocrine challenge testing

A number of studies have been undertaken to investigate the functioning of the nervous system through the use of neuroendocrine challenge tests. These tests often consist of measuring the effect of a drug on pituitary hormonal release. As the pituitary gland is regulated by the brain, this testing strategy can be considered a relatively non-invasive “window” into central nervous system functioning (3).

In support the ability of these tests to detect altered neural functioning, researchers have demonstrated changes in prolactin response following neurotoxic exposure. For example, studies have shown altered prolactin response to serotonin-related drugs following 5-HT neuron-damaging toxin exposure in monkeys (4) and rats (5,6).

Prolactin response to buspirone in ME/CFS

Buspirone is marketed as a treatment for generalized anxiety disorder, though unlike classical anxiety medications such as benzodiazepines, buspirone has no activity at GABA receptors. Instead, buspirone is an agonist of 5HT1A receptors, where it exhibits strong binding affinity, and also acts as an antagonist at dopamine D2 receptors, albeit with weaker binding affinity (7).

Strikingly, every single study that has tested prolactin response to buspirone in ME/CFS has reported that patients exhibit an abnormally large increase in prolactin about one to two hours after administration. The results of these studies are summarized below, as well as in Table 1.

The first study of prolactin response in an ME/CFS-like condition came from Bakheit et al. in 1992. The findings from this study were reported both in Bakheit's thesis (8), as well as in a peer-reviewed paper (9). The authors were studying postviral fatigue syndrome (PVFS), in which the criteria used for the study closely resembled the chronic fatigue syndrome criteria proposed by Holmes et al. (10) and Sharpe et al. (11). The study criteria also required that participants' fatigue was preceded by a probable or definite viral infection, and was made worse by exercise and did not improve after bed rest. The authors found that the patient group had a larger increase in plasma prolactin after administration of buspirone, when the patients were compared to healthy controls or individuals with depression. The same effect was observed in separate analyses of males and females. Figure 1 illustrates the study results using the individual level data provided in Bakheit's thesis. Notably, and as seen in virtually all other studies of this topic, baseline prolactin was not significantly altered in the patient group.

Further evidence was provided by John Richardson in 1995. In this study, patients who fulfilled the CDC and Oxford criteria for ME/CFS were compared to family members without

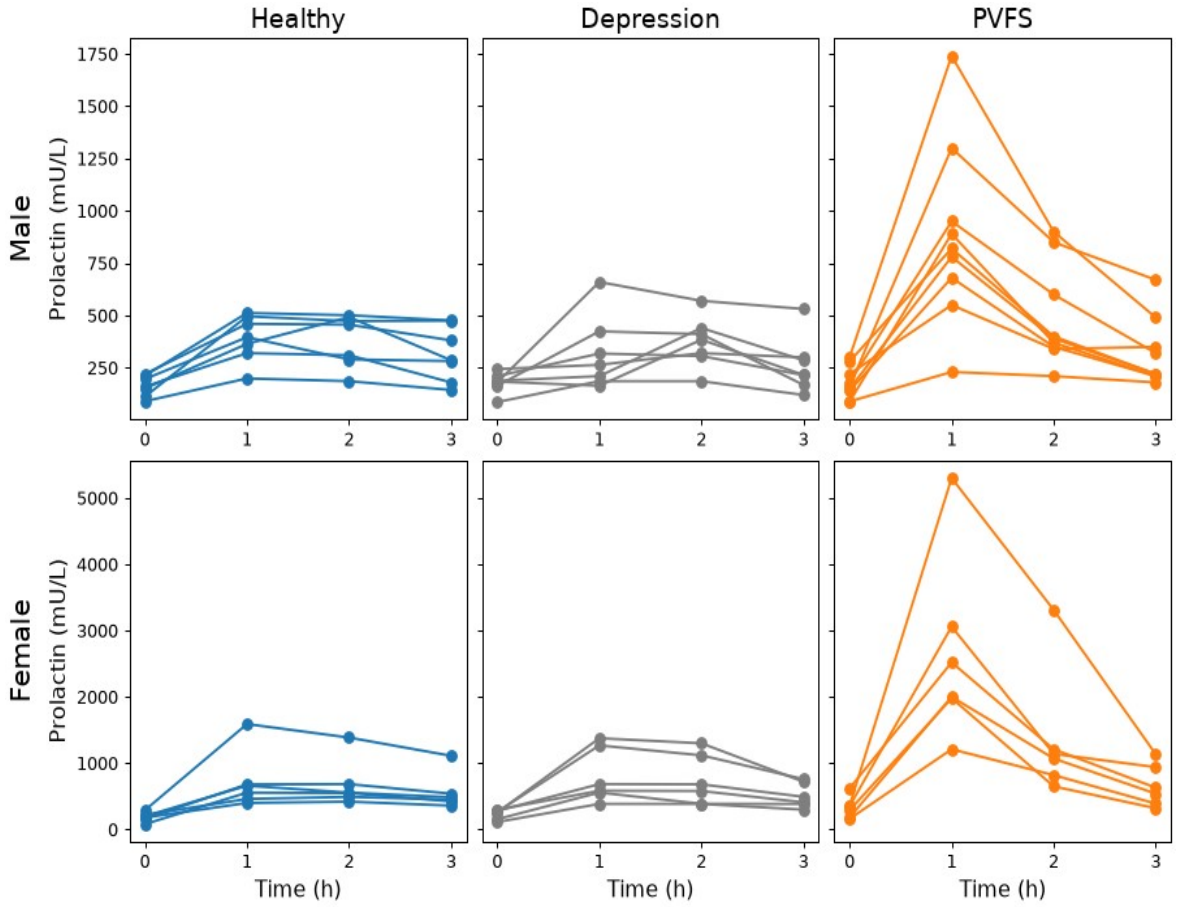

Figure 1: Prolactin response, based on data from the Bakheit's 1992 thesis.
PVFS: Postviral fatigue syndrome

ME/CFS. With prolactin response defined as the ratio of prolactin levels after to before buspirone administration, the response to buspirone (50 mg, orally) in the patients was, on average, over 3 times higher than that of the controls. The study also found a correlation between prolactin response in patients and their degree of sleep disturbance (12). A later study from Richardson and Costa again suggested very high prolactin responses to buspirone (50 mg, orally) in ME/CFS patients, however this study did not include a control group, and it is unclear if high prolactin response was a criteria for inclusion in the study (13).

In 1996, Sharpe et al. reported increased prolactin response to buspirone (0.5 mg/kg up to 45 mg, orally) in patients fulfilling Oxford criteria for ME/CFS (11), but who did not also exhibit symptoms of depression. Notably, plasma levels of buspirone and its metabolite, 1-(2-Pyrimidinyl)piperazine (1-PP), were not significantly different between groups after administration of buspirone, suggesting that the difference in prolactin response was not caused by differences in drug metabolism. The growth hormone response to buspirone did not significantly differ between groups (14).

Also in 1996, Tahir Majeed, under the supervision of Peter O. Behan, who was an author on the 1992 PVFS paper, published a thesis testing hormonal responses to a variety of drug challenges. The study cohort included patients who fulfilled Fukuda (15) and Oxford (11) criteria, and who had fatigue which worsened after exercise. The control group was made up of healthy, sex-matched volunteers. The ME/CFS patients exhibited a significantly larger increase in prolactin after administration of buspirone (60 mg, orally). Further findings in ME/CFS patients included normal growth hormone responses to bromocriptine and baclofen, a larger growth hormone response to pyridostigmine, smaller growth hormone responses to desipramine and dexamethasone, and a smaller adrenocorticotropic hormone (ACTH) response to ipsapirone (16).

Another 1996 paper, authored by Behan, reported increased prolactin response to buspirone (60 mg, orally) in individuals with an ME/CFS-like illness (including myalgia, fatigue worsened by exercise, and with onset after a flu-like illness) and who had previously been exposed to organophosphates (17). Note that while this paper indicates that the study included 10 male healthy controls, later court testimony from Behan in an organophosphate trial indicated that there was a mistake in the paper, and the actual control group was made up of 15 males and 15 females (18). However, as Behan noted in court, the inclusion of females in the control group would not be expected to lead to spurious differences between groups, and would instead more likely have led to a smaller difference, as females have larger prolactin responses to buspirone than males (19).

Additionally, two studies from Racciatti et al. suggest that the authors have observed further evidence of increased prolactin response to buspirone in ME/CFS. However one study did not include a healthy control group (20), and the other was reported in an abstract which we have not been able to access (21), and with the findings briefly mentioned in a later review (22).

Finally, a 2001 case report from Sharma et al. reported about a female patient with ME/CFS (Oxford criteria), who exhibited an abnormally large prolactin response to buspirone (30 mg, orally). After symptom improvement, which followed a graded exercise therapy intervention, the prolactin response was measured again on two occasions, and was found to be normal both times (23).

Prolactin response to other challenges in ME/CFS

Additional evidence of abnormal prolactin response is provided by studies which tested

fenfluramine, exercise, and insulin-induced hypoglycemia in ME/CFS patients. Negative or conflicting results have been observed after administration of m-chlorophenylpiperazine (m-CPP) and tryptophan. Details of these studies are summarized below and in Table 2.

In 1995, Bearn et al. tested the prolactin response in ME/CFS to two different neuroendocrine challenges. The serotonin agonist, d-fenfluramine, was tested, but prolactin response did not significantly differ between groups. On the other hand, inducing hypoglycemia through administration of insulin led to a significantly *smaller* increase of prolactin in the ME/CFS group (24).

Ottenweller et al. tested a treadmill-based maximal exercise challenge, and again reported a significantly smaller increase of prolactin in ME/CFS patients (25).

Yatham et al. published a study of response to racemic fenfluramine in ME/CFS. In this study, the groups did not significantly differ in the magnitude of prolactin response (26).

Two later studies from separate groups tested the prolactin response to d-fenfluramine, and both of these studies reported increased prolactin response in the ME/CFS patients (27,28).

A 2001 study did not find a significant difference between ME/CFS patients and controls in prolactin response to the serotonin agonist, m-CPP (29).

Finally, a 2010 study reported a significantly increased prolactin response to the serotonin precursor, tryptophan, in females with ME/CFS, but not in females with both ME/CFS and fibromyalgia, or in either of the male patient groups (30).

Prolactin response in other conditions

Abnormally increased prolactin response has been reported in several other conditions, such as migraine, irritable bowel syndrome (IBS), hormonal disorders, and gonadal disorders. The following section includes some examples of these studies, but this review should not be considered exhaustive.

Migraine

Abnormal prolactin response has been reported several times in migraine. Migraine patients may have an abnormally long return to baseline prolactin after administration of reserpine (seen in males) (31) or benserazide (seen in females) (32). Studies have reported abnormally increased prolactin response in migraine patients to the D2 antagonists sulpiride (32,33) and domperidone (33). An abnormally large *decrease* in prolactin has been noted after administration of L-deprenyl (34). In contrast, an abnormally *small* decrease was reported after administration of the dopamine reuptake inhibitor, nomifensine (33) and the dopamine precursor, L-DOPA (35). Cassidy et al. have published two studies showing increased prolactin response to buspirone in migraine (36,37). The prolactin response to m-CPP was larger in a study that used a dosage of 0.5 mg/kg (38), but not in a study that used a smaller 0.25 mg/kg dosage of the drug (39). A larger prolactin response was noted after administration of racemic fenfluramine (40).

Several studies have tested TRH challenges in migraine. A blunted prolactin response in migraine was seen after administration of 50 μg and 200 μg doses of TRH (41). Another study found an increased prolactin response to TRH during migraine attacks (42). Awaki et al. found an abnormally increased prolactin response after administration of a cocktail which included TRH,

gonadotropin-releasing hormone (GnRH), and insulin (43).

However, other studies of migraine did not find significant differences between groups, including after administration of domperidone (44), fenfluramine (32), lisuride (33), metaclopromide (45,46), morphine (47), piribedil (48), and sumatriptan (49).

Other disorders

Several studies from the same research group have reported abnormally increased prolactin response to buspirone in IBS (50), and in non-ulcer dyspepsia (51–54).

An increased prolactin response was seen in primary testicular failure after administration of TRH (55) and metoclopramide (56). Prolactin response to TRH was also significantly larger in females with primary ovarian failure (57). An increased prolactin response to TRH was also reported in patients with polyendocrine metabolic ovarian syndrome (PMOS) (58).

Additionally, some studies have reported observing health conditions in which patients demonstrated *blunted* prolactin responses. For example, the prolactin response to buspirone or fenfluramine has been observed to be blunted in depression patients in some (27,59), but not all studies (60).

Connection to sex hormones?

As females are more likely than males to have ME/CFS (61), it may be useful to consider whether sex hormones influence prolactin response in a way that may explain the observations of increased prolactin response to buspirone and d-fenfluramine in ME/CFS.

Healthy females have a higher prolactin response to buspirone than males (19). Similar sex differences have been observed after administration of thyrotropin-releasing hormone (TRH), phenothiazine, and possibly chlorpromazine (62–64). These findings suggest an intriguing connection to the prolactin response and sex bias seen in ME/CFS.

Prolactin response to various drugs also differs throughout the menstrual cycle. While baseline prolactin levels stayed relatively steady throughout the menstrual cycle, it was observed that prolactin response to d-fenfluramine was highest at mid-cycle, followed by luteal, then follicular phases. This mirrored the differing amounts of circulating estradiol present across the menstrual cycle (65). Prolactin response to buspirone in females was found to be larger during the luteal phase than during the follicular phase or mid-cycle (19). Prolactin response to TRH may be somewhat larger during the follicular phase (66), but findings are inconsistent (67).

Exogenous estradiol can modulate prolactin response. TRH-induced prolactin response is substantially larger in females taking a short course of exogenous estradiol, as well as after subsequent short-term combined contraceptive use, but not in those taking long-term combined contraceptives (66). In male rats, a prolactin response to TRH was only detectable when the rats had previously been administered estradiol (68). Exogenous estradiol also causes an increased prolactin response to ghrelin in postmenopausal women (69). Further, administration of estradiol to overiectomized rats caused substantially larger prolactin responses to the dopamine antagonist, thioproperazine (70).

Dinan et al. also reported that females had more symptoms of sedation in response to buspirone during the luteal phase than at other timepoints, with this being the timepoint where prolactin response was found to be highest (19). This may relate to the finding that ME/CFS patients appear to have more buspirone-induced side effects, such as fatigue and nausea, when compared to healthy controls (9,12,14).

Like ME/CFS (61), migraine appears to be more prevalent in females than males (71,72). As

noted in the “Migraine” section, this is one of the few other health conditions in which several studies have reported increased prolactin response to various neuroendocrine probes, including buspirone. These commonalities may suggest similar underlying pathways related to sex hormones in these health conditions.

An important point to keep in mind is that a hypothesis which ties estradiol to the abnormal prolactin response seen in ME/CFS would need to be explained by a mechanism which is independent of blood estradiol levels, as studies have shown that blood levels of this hormone do not appear to be significantly increased in ME/CFS (73–76). One alternative possibility was proposed in a study of increased prolactin response to TRH in primary ovarian failure, where the authors speculated that the patients might have increased conversion of androgens to estrogens within the hypothalamus (57). This was not based on direct evidence, so should be interpreted cautiously, but it may be worth considering this possibility.

Where to go from here?

The implications of abnormal prolactin response in ME/CFS are far from clear. While several of the ME/CFS prolactin response papers suggested that the findings were evidence of abnormalities in the serotonin system (9,16,27,28), there is still too little direct evidence to make strong conclusions about specific systems. Indeed, a PET study of serotonin receptors in ME/CFS resulted in the opposite of what the authors had expected based on prior prolactin response findings (they found down-regulation instead of up-regulation of 5-HT1A receptors) (77). Serotonin-related drugs, which were used in most of the ME/CFS studies with significant results, are unlikely to be able to directly stimulate lactotrophs (78), and may instead exert at least part of their influence on lactotrophs through altering hypothalamic dopamine release (79). Thus, while abnormal prolactin response could be explained by changes in the receptors directly affected by the neuroendocrine probes, such as 5-HT receptors, these findings could instead be highlighting any of a number of possible downstream abnormalities, such as alterations in dopamine functioning or sensitization of lactotrophs.

What is clear is the importance of further exploration of these findings. ME/CFS is a condition with notoriously few well-replicated, specific findings. Some of other relatively replicated findings include female sex bias (61) and decreased NK cell cytotoxicity (80), but these findings have not yet led to usable insights into pathophysiology or treatment development. With so few clues into the underlying pathophysiology, it is important to thoroughly investigate every available avenue.

A straightforward next step would be testing prolactin response to other neuroendocrine probes. For example, if dopaminergic drugs and TRH both lead to abnormal prolactin responses, this would suggest abnormally sensitized lactotrophs, as dopamine and TRH both directly affect lactotrophs (2). On the other hand, if neither of these probes demonstrates altered responses, but responses to serotonin-related drugs are altered, this may indicate upstream abnormalities. It may be most fruitful to consider testing the probes which have already been reported to cause increased prolactin response in other health conditions, such as the D2 antagonist domperidone, This drug has demonstrated an increased prolactin response in one study of migraine (33), and can modulate prolactin release from the pituitary gland without appreciably crossing the blood-brain barrier (81), avoiding the interpretation challenges associated with drugs that interact with the central nervous.

One ME/CFS study has reported increased levels of alpha-melanocyte-stimulating hormone (α-MSH), albeit with substantial overlap between groups (82). α-MSH is known to alter prolactin

response, both in vitro and in vivo in non-human animals (83–86). Thus, it may be worthwhile to attempt to replicate increased α-MSH in ME/CFS, and to test for a correlation to prolactin response in these patients.

One could test the estradiol hypothesis outlined in the previous section by measuring the prolactin response to buspirone or another probe in ME/CFS and healthy controls both before and after administration of an estrogen receptor antagonist or aromatase inhibitor. If the difference between groups were found to be diminished after blocking the influence of estrogens, this would provide evidence of sex hormone involvement in the abnormal prolactin response. It may be necessary to prescribe an extended course of these drugs prior to the second prolactin challenge, as estrogens are capable of inducing long term changes in prolactin-secreting cells, for example through genomic regulation or by increasing the number of lactotrophs, as reviewed by Grattan et al. (1).

It may also be possible to explore this finding further using PET scans, for example by measuring dopamine receptor D2 (DRD2) binding in the pituitary gland. If the ME/CFS abnormality does relate to sex hormones, then DRD2 levels may be altered, as is seen when estradiol is applied to anterior pituitary cells in vitro (87).

Controlling for confounders

To ensure interpretable results, and to increase the likelihood of detecting real differences, one must be mindful to control for potential confounders when studying prolactin response in ME/CFS.

One of the most important factors to consider in studies of prolactin response is the sex of participants. As noted earlier, females demonstrate larger prolactin responses than males (19). Thus, at minimum, case and control groups should have the same ratio of females to males. However, it may be wise to also control for sex in an appropriate statistical model or analyze males and females separately to reduce the influence of variance associated with sex.

Additionally, as females exhibit variance in prolactin response throughout the menstrual cycle (19,65), researchers should consider controlling for this factor as well. Some of the clearest differences between ME/CFS and healthy participants occurred in studies of females tested during the luteal phase (9,12), while a study that included females tested during the follicular phase showed a smaller group difference (16). While one can not make strong conclusions about menstrual phase effects from such limited data, this may suggest that the optimal time for testing females is during the luteal phase. However, if females in different stages of the menstrual cycle are tested within the same study, this variable should be controlled for.

It may also be worthwhile to control for the effects of additional placebo-like factors on prolactin response (88). As stress can cause changes in prolactin secretion (89,90), this factor could potentially play a role in ME/CFS findings, for example through the stress associated with venipuncture. Though, at least one study has tested prolactin response to placebo in ME/CFS, and found that patients did not exhibit an abnormally increased prolactin response following the placebo test (29).

Sedentariness associated with ME/CFS may also play a role in abnormal prolactin response. One study suggested that sedentary individuals exhibit an increased prolactin response to buspirone, when compared to endurance-trained athletes (91), while another study found no difference between groups in a d-fenfluramine prolactin challenge (92). To decrease the potential influence of sedentariness on results, researchers may wish to include non-ME/CFS controls matched for physical activity level.

Further, researchers should ensure that other significant medical conditions which could influence prolactin response are not present in the study cohort. For example, liver and kidney diseases affect metabolism of buspirone (93), and this may alter prolactin response to this drug. Even if such disorders are excluded, it may still be worthwhile to test for plasma concentrations of neuroendocrine probes to avoid confounding due to differences in drug metabolism. Also, as some studies have suggested blunted prolactin response in depression (27,59), it may be beneficial to exclude participants with comorbid depression, to reduce the likelihood of masking an ME/CFS-associated increased prolactin response.

Reviving a forgotten thread

Almost all studies of abnormal prolactin response in ME/CFS were conducted in the 1990s, with no studies directly testing prolactin response in ME/CFS in over 15 years. The literature does not appear to suggest that anyone has argued that ME/CFS findings were misleading or false positives.

Duval et al. argue that neuroendocrine challenge testing, at least in the field of psychiatry, was largely abandoned in recent years for a few reasons, including the difficulties of controlling for all relevant confounding influences on hormones, difficulty in recruiting drug-naive participants, and the lack of interpretability afforded by readily available but non-specific probes (94). One can imagine that prolactin response research in ME/CFS may have been a casualty of the pivot away from neuroendocrine research in other fields.

Considering the massive burden of ME/CFS, both in terms of prevalence as well as the substantial suffering imposed on individuals, the importance of continuing this research is clear. Through careful consideration of study design and consultation with experts in endocrinology and neurology, future research into prolactin response may uncover important insights into the pathophysiology of ME/CFS, a condition which has, so far, eluded explanation.

Table 1: Studies testing prolactin response to buspirone in ME/CFS-like conditions

Study	Participants	Probe	Prolactin response*	Notes
Bakheit, 1992 (8) (Thesis, supervised by Peter O. Behan) Bakheit et al., 1992 (9)	6F, 9M PVFS 6F, 7M depression 6F, 7M healthy	Buspirone (60 mg, orally)	PVFS: **8.2 (females)** and **5.0 (males)** Depression: 3.6 (females) and 2.1 (males) Healthy: 3.9 (females) and 2.5 (males)	Females tested during luteal phase. Only PVFS participants experienced excessive fatigue, lightheadedness, and nausea after buspirone. Minor data inconsistencies for a small number of participants, likely due to transcription errors, were noted (95), but these are unlikely to meaningfully affect the conclusion.
Richardson, 1995 (12)	25F, 5M CFS/ME (Oxford) 30 healthy (details of sex not reported)	Buspirone (50 mg, orally)	**CFS/ME: 4.9** Healthy: 1.8	Females tested during luteal phase. Patients experienced more nausea after buspirone compared to controls.
Sharpe et al., 1996 (14)	11M CFS (Oxford) 11M healthy	Buspirone (0.5 mg/kg up to 45 mg, orally)	**CFS: 2.9** Healthy: 2.4	Growth hormone response was not significantly different between groups. Patients had more nausea in response to buspirone but this did not correlate with prolactin response. Plasma levels of buspirone and its major metabolite, 1-PP, were not significantly different between groups.
Behan, 1996 (17)	10M CFS with previous exposure to organophosphates. 15F, 15M healthy from previous study	Buspirone (60 mg, orally)	**CFS: 4.8** Healthy: 1.9	The paper was later found to include an error: the control group was incorrectly described as 10 males. (18) Patients also had increased GH response to pyridostigmine and decreased GH response to dexamethasone.
Majeed, 1996 (16) (Thesis, supervised by Peter O. Behan)	15F, 15M CFS (Fukuda) 15F, 15M healthy	Buspirone (60 mg, orally)	**CFS: 2.8** Healthy: 2.0	Females tested during follicular phase. All participants had been medication-free for at least 3 months. No participants reported nausea after buspirone. Other studies within the thesis found: normal GH responses to bromocriptine and baclofen, larger GH response to pyridostigmine, smaller GH responses to desipramine and dexamethasone, and smaller ACTH response to ipsapirone.
Racciatti et al., 2001 (20)	3F, 2M CFS after toxic exposure 3F, 1M CFS after EBV 4F, 1M CFS with depression No healthy controls	Buspirone	"[…] an abnormal increase of prolactine levels followed the buspirone challenge test […] in all the three subgroups of patients."	Prolactin values and buspirone dosage not included in paper.
Sharma et al., 2001 (23)	1F CFS (Oxford)	Buspirone (30 mg, orally)	CFS: 10.9 After symptom improvement following graded exercise program: 12 months: 2.1, 18 months: 1.2	Case study.

F: Females; M: Males; PVFS: Postviral fatigue syndrome; CFS: Chronic fatigue syndrome; ME: Myalgic encephalomyelitis; GH: Growth hormone; EBV: Epstein-Barr Virus; Fukuda: Fukuda et al., 1994 (15); Oxford: Sharpe et al., 1991 (11); Holmes: Holmes et al., 1988 (10); 1-PP: 1-(2-pyrimidinyl)piperazine

*Prolactin response was calculated as peak average prolactin divided by average prolactin at timepoint 0. Data were approximated from plots using WebPlot Digitizer 4 when exact values were not reported. Bolding indicates that the group was significantly different from the healthy control group for prolactin response. Note that the definition of response for the purpose of significance testing varied by study, and does not necessarily correspond to the definition used in this table.

Table 2: Studies testing prolactin response to probes other than buspirone in ME/CFS-like conditions

Study	Participants	Probe	Prolactin response*	Notes
Cleare et al., 1995 (27)	4F, 6M CFS (Holmes and Oxford) 4F, 6M depression 8F, 12M healthy	D-fenfluramine (30 mg, orally)	**CFS: 1.5** Depression: 0.9 Healthy: 1.2	Females tested during follicular phase. Cortisol response did not differ from healthy group. When analyzing full cohort, baseline cortisol inversely correlated with prolactin response.
Bearn 1995 (24)	4F, 5M CFS (Oxford and all but one fulfilled Holmes) 6F, 4M healthy	D-fenfluramine (30 mg, orally)	CFS: 1.5 Healthy: 1.7	Females tested on days 3-5 of their menstrual cycle. ACTH response was greater in patients. Cortisol response showed no group difference.
Bearn 1995 (24)	4F, 5M CFS (Oxford and all but one fulfilled Holmes) 6F, 2M healthy	Insulin (0.1 or 0.15 u/kg)	**CFS: 5.1** Healthy: 6.7	Females tested on days 3-5 of their menstrual cycle. Growth hormone response trended lower in patients. Cortisol and ACTH responses were not significantly different.
Yatham et al., 1995 (26)	8F, 3M CFS (Holmes) 8F, 3M healthy	DL-fenfluramine (60 mg, orally)	CFS: 1.7 Healthy: 2.5	Cortisol response did not significantly differ between groups.
Sharpe et al., 1997 (28)	10M CFS + neurasthenia 10M healthy	D-fenfluramine (30 mg, orally)	**CFS: 1.6** Healthy: 1.1	
Ottenweller et al., 2001 (25)	17F CFS (Holmes and Fukuda) 14F healthy	Maximal exercise test on treadmill	**CFS: 1.2** Healthy: 2.2	Females tested during luteal phase. ACTH, EPI, TSH, DHPG, DOPA, and DOPAC responses were lower, GH response was higher, and NE response not significantly different.
Vasallo et al., 2001 (29)	16F, 4M neurasthenia (all but one also fulfilled Oxford and CDC criteria) 15F, 5M healthy	m-CPP (0.25 mg/kg, orally)	Average prolactin values not reported, thus ratio could not be calculated. No significant difference between groups.	Females tested during early follicular phase. Participants also underwent a placebo test which did not raise prolactin in either group.
Weaver et al., 2010 (30)	15F, 7M CFS (Fukuda) 8F, 3M CFS (Fukuda) + FM 10F, 6M healthy	L-tryptophan (120 mg/kg lean body mass)	CFS: **2.3 (females)** and 2.2 (males) CFS+FM: 2.0 (females) and 3.0 (males) Healthy: 1.9 (females) and 2.2 (males)	Females tested during late follicular phase (days 7–14).

F: Females; M: Males; CFS: Chronic fatigue syndrome; ACTH: Adrenocorticotropic hormone; GH: Growth hormone; NE: Norepinephrine; EPI: Epinephrine; Fukuda: Fukuda et al., 1994 (15); Oxford: Sharpe et al., 1991 (11); Holmes: Holmes et al., 1988 (10); FM: Fibromyalgia; m-CPP: m-chlorophenylpiperazine

*Prolactin response was calculated as peak average prolactin divided by average prolactin at timepoint 0. Data were approximated from plots using WebPlot Digitizer 4 when exact values were not reported. Bolding indicates that the group was significantly different from the healthy control group for prolactin response. Note that the definition of response for the purpose of significance testing varied by study, and does not necessarily correspond to the definition used in this table.

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Updates

Version 1 – August 20, 2026.

Version 2 – August 21, 2026: Fixed citation for sentence about *“increased conversion of androgens to estrogens within the hypothalamus”*. Minor clarifications and style improvements.

Version 3 – August 27, 2026: Added tables, sections about confounding and neuroendocrine challenge testing, expanded conclusion, and made other minor style improvements.

Version 4 – August 29, 2026: Added email address, improved figure, and other minor improvements.

See all versions at https://github.com/ruvilonix/prolactin-response/.