

# Prescribing for patients with chronic fatigue syndrome

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**Chronic fatigue syndrome, also known as myalgic encephalomyelitis, can be difficult to both diagnose and treat, but there are many prescribed medications that can help with specific symptoms and co-morbidities. This article provides a guide to treatment in primary care.**

**C**hronic fatigue syndrome (CFS), synonymous with myalgic encephalomyelitis (ME),<sup>1,2</sup> can be defined as a debilitating fatigue affecting mental and physical function, lasting at least four months in an adult and three months in a child or adolescent,<sup>1</sup> in conjunction with at least four of the following symptoms:

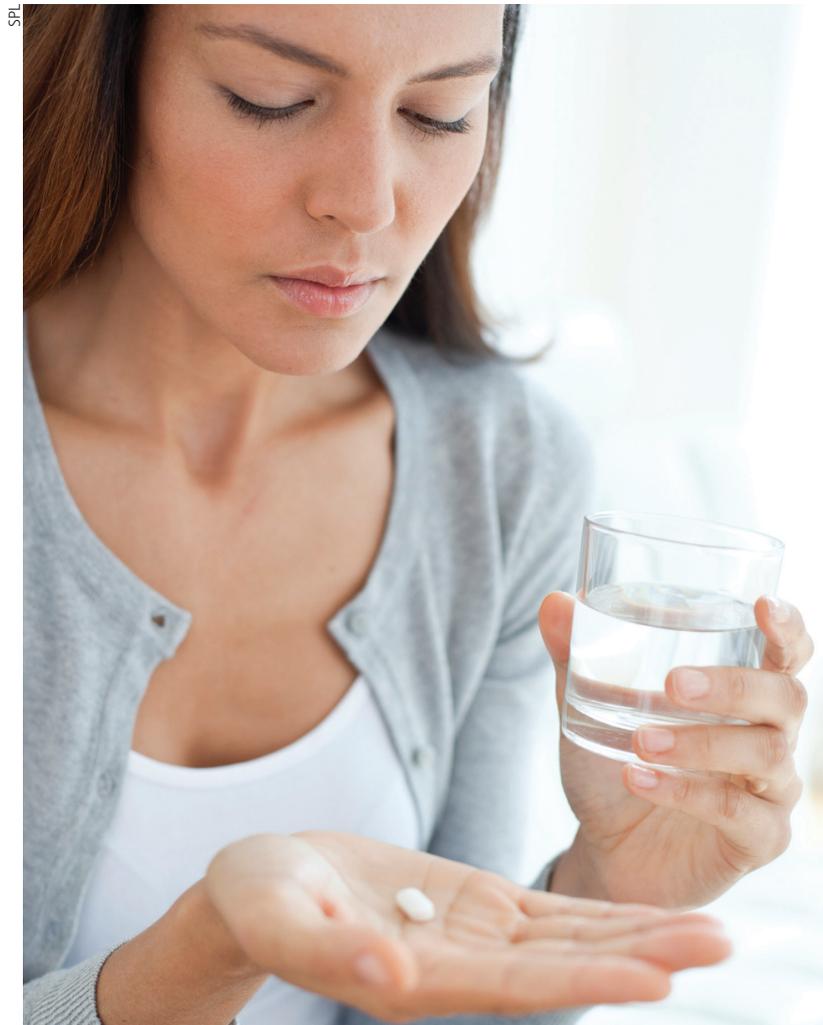
- Post-exertional malaise and fatigue
- Myalgia
- Polyarthralgia
- Impaired memory and cognitive disturbance
- Unrefreshing sleep
- Persistent/recurrent sore throat
- Tender cervical or axillary lymph nodes.<sup>3</sup>

Effective management includes graded exercise therapy (GET) and cognitive behavioural therapy (CBT) along with treating the specific symptoms individually. The NICE guideline on CFS/ME was published in 2007<sup>1</sup> and is currently being reviewed. It is expected that the new guideline will be published in 2020.

## Aetiology and prevalence

CFS/ME affects women three to five times more than men (analogous to the sex preponderance seen in autoimmune diseases) with the majority of cases occurring between the ages of 40 and 59 years.<sup>4</sup> However, there are two distinct peaks at 10–19 years and 30–39 years.<sup>5</sup> The gender distribution is about equal before puberty.<sup>6</sup> In primary care in the UK, the patient prevalence of CFS/ME is around 2.6%.<sup>7</sup>

Despite extensive research, the aetiology of CFS/ME has remained elusive, but it appears to be multifactorial, including a genetic susceptibility and environmental factors. It has been postulated that it could be due to an immunological dysfunction or there may be an inflammatory basis to it.<sup>8</sup> Treatments targeting this have shown some promise but are very much in the early stages of development.



### Diagnosis

Diagnosis is not easy and is by exclusion. There is no specific diagnostic test for CFS/ME, and it causes no specific changes in the body that can be measured or detected consistently.

A diagnosis of CFS/ME may be made from the symptoms described in the introduction above and on exclusion of the following conditions:

- Depression as a primary cause of fatigue
- Polymyalgia
- Hypothyroidism
- Diabetes mellitus.

A diagnosis of CFS/ME should be reconsidered if at least one of the following is absent:<sup>1</sup>

- Post-exertional malaise
- Cognitive disturbance
- Sleep disturbance.

### Investigations

An initial routine screen for patients presenting with CFS/ME should be carried out, as recommended in the NICE guideline,<sup>1</sup> and further investigations undertaken if indicated. A complete history (including exacerbating and alleviating factors, sleep disturbance and inter-current stressors) should be taken. A general physical examination and an assessment of psychological well-being should also be carried out.

NICE recommends the following tests:<sup>1</sup>

- Urinalysis for protein, blood and glucose
- Full blood count
- Urea and electrolytes
- Liver function
- Thyroid function
- Erythrocyte sedimentation rate or plasma viscosity
- C-reactive protein
- Random blood glucose
- Serum creatinine
- Screening blood tests for gluten sensitivity
- Serum calcium
- Creatine kinase
- Serum ferritin levels (children and young people only).

NICE also suggests the use of clinical judgement when deciding on additional investigations to exclude other diagnoses. Tests for serum ferritin in adults should not be carried out unless a full blood count and other haematological indices suggest iron deficiency. Tests for vitamin B12 deficiency and folate levels should not be carried out unless a full blood count and mean cell volume show a macrocytosis.<sup>1</sup> NICE adds that the following tests should not be done routinely to aid diagnosis:<sup>1</sup>

- The head-up tilt test
- Auditory brainstem responses
- Electrodermal conductivity.

Antidepressant	Recommended dosage	Comments
<i>SSRIs and SNRIs</i>		
Fluoxetine	Start at 20mg and increase gradually	Side-effects of decreased alertness, sexual problems (common to all SSRIs/SNRIs)
Citalopram	Start at 20mg daily	Particularly useful in the elderly, and with concomitant anxiety
Paroxetine	Start at 20mg daily	
Duloxetine	Start at 60mg daily	
<i>Tricyclic antidepressants</i>		
Amitriptyline	Start at 10mg at night and increase gradually to 150mg, as required, for both	Antimuscarinic side-effects and worsening orthostatic symptoms may necessitate a change to SSRIs. But if tolerated, may have a beneficial effect on chronic pain symptoms and migraine
Nortriptyline		
<i>Anticonvulsants</i>		
Pregabalin	Start at 75mg twice daily increasing to 225mg twice daily as needed	May be prescribed as an alternative to antidepressants for co-occurring pain, mood regulation or sleep disruption, although effectiveness is limited <sup>11</sup>
Gabapentin	Start at 300mg once daily initially, increase gradually according to response, maximum 2400mg daily given in three divided doses <sup>11</sup>	

**Table 1.** Medications used for the treatment of depression in chronic fatigue syndrome/myalgic encephalomyelitis

Serological testing should not be carried out unless the history is indicative of an infection. Depending on the patient's history, tests for the following infections may be appropriate:<sup>1</sup>

- Chronic bacterial infections, such as borreliosis (Lyme disease)
- Chronic viral infections, such as HIV or hepatitis B or C
- Acute viral infections, such as infectious mononucleosis (use heterophile antibody tests)
- Latent infections, such as toxoplasmosis, Epstein-Barr virus or cytomegalovirus.

### Referral to a specialist

The NICE guideline recommends that all patients presenting with CFS/ME should be offered a referral to a specialist.<sup>1</sup> The timescale depends on CFS/ME symptom severity:

- Mild symptoms – refer within six months of presentation
- Moderate symptoms – refer within three to four months of presentation
- Severe symptoms – refer immediately.

### Treating CFS/ME in primary care

The NICE guideline recommends that the treatment of CFS/ME should involve a considerable amount of reassurance and support, as well as the use of non-pharmacological treatments, such as CBT or GET.<sup>1</sup> However, pharmacological therapy also has a role to play in managing individual symptoms and co-morbidities. CFS/ME is often accompanied by the following conditions, the adequate treatment of which would improve quality of life for patients with this very debilitating condition.

#### Depression and anxiety

Similar to other chronic conditions, the prevalence of depression or anxiety (or both) in CFS/ME is around 40%.<sup>9</sup> Co-morbid depression is best treated with selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs) or tricyclic antidepressants (see Table 1). If sleep disturbance is a prominent feature of depression, trazodone may be used (for insomnia). A benzodiazepine (eg clonazepam) may be used for anxiety symptoms but this should be short-term use only, due to the risk of dependence. With all antidepressants, improvement in symptoms may take at least two to three weeks, if not longer. The more severe the symptoms, the longer it takes to see a response.<sup>10</sup>

Anticonvulsant medications (eg pregabalin, gabapentin), typically used in the treatment of neuropathic pain conditions, may be prescribed as an alternative to antidepressants for co-occurring pain, and to address issues such as mood regulation and sleep disruption, although their effectiveness is limited.<sup>11</sup>

#### Pain and myalgia

There is little evidence that symptoms such as pain, fatigue or sleep disturbance are positively affected by SSRIs. Pain or myalgia is best treated with analgesics. The lowest effective dose should be prescribed (see Table 2).

Medication	Dosage	Comments
Paracetamol	500–1000mg 8 hourly, as required	Often ineffective
Aspirin	300–600mg 6–8 hourly, as required	Often ineffective
NSAIDs Diclofenac Naproxen	75–100mg daily 500–1000mg daily	Often ineffective. May exacerbate gastritis or reduce renal function
Tricyclic antidepressants		Helpful for most chronic pain, see sleep section and Table 3
Duloxetine	20–90mg daily	May increase sweating, blood pressure or heart rate
Narcotics	Avoid if possible	Side-effects include constipation and habituation. Narcotics are best avoided for chronic pain
Tramadol	50–100mg 6–8 hourly	Seizure risk and interaction with drugs that raise serotonin

**Table 2.** Medications used for the treatment of pain in chronic fatigue syndrome/myalgic encephalomyelitis<sup>2</sup>

#### Migraine

Migraine appears to be present in nearly 70% of patients with CFS/ME.<sup>12</sup> A trial of a triptan should be considered. If the headaches are of the chronic daily type, topiramate may be effective, especially if the headache occurs more than three times a week.

Dosage recommendations are as follows:

- Sumatriptan: 25–100mg orally as a single dose, may repeat in two hours; maximum 200mg daily
- Zolmitriptan: 1.25–5mg orally as a single dose, may repeat in two hours if necessary, maximum 10mg daily
- Topiramate: 25mg orally once daily at night initially, increase gradually according to response, maximum 100mg daily given in two divided doses.<sup>11</sup>

#### Sleep disturbance

Medication for sleep should, as far as possible, be safe for long-term use and started at a lower dose and increased gradually (see Table 3). Sleep apnoea should be excluded before commencing treatment.

#### Recurrent flu-like symptoms and sore throat

Nasal symptoms such as congestion and rhinorrhoea may respond to frequent use of over-the-counter nasal saline sprays and menthol gels. Anticholinergic drugs such as ipratropium can reduce rhinorrhoea. Only products that are indicated for mucosal use should be used in order to avoid damaging the

Medication	Dose	Comments
Tricyclic antidepressants: amitriptyline, doxepin, nortriptyline	5–100mg	Take one to two hours before bedtime. May worsen dry mouth, constipation or orthostatic intolerance, or cause daytime sedation
Trazodone	12.5–200mg	May be the least likely to lose effectiveness for sleep
Quetiapine	12.5–100mg	May cause weight gain or extrapyramidal symptoms
Gabapentin	100–1500mg	May help nocturnal pain and restless legs syndrome
Pregabalin	50–450mg	Helpful for nocturnal pain, but very sedating for some
Antihistamines Promethazine Diphenhydramine	10mg 50mg	Anticholinergic side-effects
Clonazepam	0.25–1mg	For restless legs, muscle spasms or anxiety
Orphenadrine	100mg	For restless legs or muscle spasms
Ropinirole/pramipexole	0.125–0.25mg	For restless legs or muscle spasms
Melatonin	2mg 1–2 hours before bedtime (or as advised by specialist)	May help patients who have altered circadian rhythms. Needs to be initiated by a specialist
Zolpidem	2.5–10mg	Short duration of action may lead to rebound insomnia
Zopiclone	7.5mg	Short duration of action may lead to rebound insomnia
Mirtazapine	7.5–15mg	May cause daytime sedation; tolerance may develop

**Table 3.** Medications for aiding sleep in chronic fatigue syndrome/myalgic encephalomyelitis<sup>2</sup>

nasal epithelium. Nasal decongestant sprays such as oxymetazoline should be avoided because of the risk of rhinitis medicamentosa (rebound congestion). However, olopatadine, an antihistamine nasal spray, protected against vasomotor challenge in one small study of people with severe vasomotor rhinitis. Phenylephrine had a small benefit on working memory during tilt-table testing in patients with CFS/ME, but cannot be recommended as a therapy.<sup>11,13</sup>

*Impaired memory (cognitive dysfunction)*

No pharmacological agents are recommended for the treatment of symptoms relating to memory disturbances or disturbances of cognition. Several drugs have been tried experimentally but no significant improvement has been demonstrated.

The following drugs should not be used for the treatment of CFS/ME,<sup>1</sup> especially for the treatment of fatigue or memory symptoms:

- Monoamine oxidase inhibitors
- Glucocorticoids (such as hydrocortisone)
- Mineralocorticoids (such as fludrocortisone)

- Dexamfetamine
- Methylphenidate
- Thyroxine
- Antiviral agents.

**Prognosis**

The long-term outcome for CFS/ME is disappointing. Chances of complete recovery in children and young adolescents are better than in adults.<sup>14</sup> Studies have shown that between 17% and 64% of all patients improve with treatment; however, full recovery occurs in fewer than 10% of patients and 20% may actually worsen.<sup>11,15</sup>

**Complementary and alternative medicine**

The NICE guideline states clearly that there is insufficient evidence that complementary therapies are effective treatments for CFS/ME and therefore their use is not recommended. However, some people with CFS/ME choose to use some of these therapies for symptom control and find them helpful.<sup>1</sup>

There is little evidence of any benefit from complementary

medicine, such as massage therapy, non-stressful exercises and homeopathic treatment. There may be some benefit from Chinese medicine;<sup>16</sup> however, the evidence is not strong, and findings need to be confirmed by well-designed, randomised double-blind controlled trials. Until more evidence is available, such approaches are not recommended for the treatment of CFS/ME.

## Conclusion

CFS/ME is a debilitating condition with no known cure, which can present with varying degrees of severity. Its effects can be mitigated by various interventions individually or in combination. However, until a cause is found, a lasting cure will remain elusive. Strong reassurance and non-pharmacological therapies (CBT and GET) remain the best options so far.

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## Declarations of interest

None to declare.

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