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# Tired all the time

## *Most cases are managed in primary care—where the research needs to be done*

General practitioners often see a syndrome they call "tired all the time." How often doctors see it depends on how tiredness is defined and where it is measured. Morrell recorded fatigue as the most important reason for consultation in 24 per 2000 registered patients in one year[1]; Jerrett recorded fatigue as a presenting or supporting symptom in 150 per 2000 registered patients.[2] Yet patients may not necessarily mention fatigue when they consult. A survey of patients waiting in one surgery found that a tenth reported "substantial fatigue" for a month or more[3]; 18-34% of respondents in a community survey reported always feeling tired in the past month[4]; and when young women patients were asked to record symptoms in diaries 400 episodes of fatigue were recorded for every one reported to the doctor.[5] Clinicians may regard this iceberg as a puzzle, and a blessing. But how should they manage the cases that do present?

Little has been published on tiredness in primary care, with only one prospective study from Britain[2] and two retrospective ones from American family practice.[6,7] The results suggest that psychosocial causes are paramount in 40-51% of cases and physical causes in 21-39%.[2,6,7] The remaining cases are of mixed or undetermined cause. Fatigue presents three times more often in women of childbearing age,[2] who often have a working day that is long and difficult to organise, with no boundary between home and work.[8] The wise doctor steers between the extremes of trivialising and medicalising such "social" fatigue. If the cause is existential rather than medical counselling may help the patient consider various alternatives and make new choices.

General practitioners are most likely to miss psychological distress when patients present with apparently physical symptoms,[9] and the psychological symptoms then continue for longer than when the cause is correctly identified.[10] Although fatigue is a physical symptom, it is also a feature of depression,[11] so patients should be asked about change in appetite, weight, sleep, and ability to concentrate. Positive responses do not necessarily exclude organic or social causes.[12] If patients are convinced that symptoms are organic it is reasonable to examine and investigate while opening up a discussion of psychosocial causes. Patients will be relieved that their concerns are addressed, and sometimes they will piece together occult worries and mention them later. When the general practitioner does identify depression, antidepressants given in therapeutic doses help.[13]

Particular physical causes depend on age and gender. In young women fatigue may be the presenting symptom of anaemia or pregnancy. In young people of both sexes it may be the presenting feature of glandular fever or some other infection.[6] It is therefore worth inquiring about menorrhagia or a missed period and symptoms of infection. With young patients a blood count, monospot test, and pregnancy test are the investigations with the highest yield.[6] Among older people fatigue is more commonly associated with circulatory disorders or, importantly, prescribed drugs, so all medications should be inquired about.[2] Occasionally fatigue may be an early symptom of endocrine or malignant disease, but these medical firm "classics" are rare in primary care. Laboratory tests generally have a low yield and clinch the diagnosis in only 8% of patients.[7] Less than 2% of patients with fatigue are referred to specialists,[1] so inferring from research done in secondary care about causal probabilities in general practice is inappropriate.

When general practitioners record fatigue as a "diagnosis" at the end of the consultation patients consult on average only 1·4 times.[14] A few, however, complain of fatigue for much longer. This condition, sometimes called myalgic encephalitis (ME), is the subject of confusion and debate. Some definitions conflate ideas about cause when the cause is not yet known, and different definitions make it difficult to compare the results of research. A consensus group has proposed that severe fatigue lasting for more than six months in the absence of certain clinical conditions should simply be called the chronic fatigue syndrome.[15] So far most of the suggested causes have not been confirmed, such as Coxsackie virus infection[16,17] and peripheral nerve dysfunction.[18,19] A few patients do have signs of immunological dysfunction after infectious mononucleosis,[20] but Wessely and Powell found that 72% of patients referred over seven months at the National Hospital for Nervous Diseases with unexplained chronic fatigue had psychiatric disorders, particularly depression.[21]

Doctors' uncertainties about the cause and prognosis of chronic fatigue may strain the doctor-patient relationship. General practitioners should acknowledge their uncertainty and keep an open mind; the patient's condition and scientific knowledge may change. Some patients will need long term support. Cognitive behaviour therapy has led to improvement in symptoms,[22] and its potential benefit warrants assessment in a randomised trial.

Whether it is subacute or chronic, the tired all the time syndrome is a clinical challenge in general practice, and it is clinicians in primary care who need to research the condition and apply the results.

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# Sumatriptan in migraine

## *May be better than aspirin and metoclopramide*

Migraine disables. Conventional treatment provides only moderate relief of symptoms, and many patients cannot work for 12 to 48 hours. The principal aims of treating acute attacks are to control pain, nausea and vomiting, and other concomitant symptoms of migraine, thereby achieving the prompt return of the patient to normal activities. Rest, simple analgesics, ergotamine, or non-steroidal anti-inflammatory drugs combined with antiemetics such as metoclopramide or domperidone are the mainstays of traditional treatment. The introduction of sumatriptan, a serotonin-1 ($5HT_1$) agonist, for acute attacks heralds a new pharmacological approach to treatment, derived from fundamental studies on receptor mechanisms that shed light on the pathogenesis of headaches.

The innervation of pain sensitive dura and vessels is through the trigeminal nerve and the upper three cervical nerve roots. On the afferent side there is a "centre" in the upper cervical cord. Pain fibres descend in the spinal root of the trigeminal nerve to C2, where they converge with afferents from C1-C3 on second order neurones. This provides a pain pathway from the head to the neck and vice versa.[1] The raphe nuclei and locus coeruleus project rostrally to the cortex and caudally as part of the "endogenous pain control circuit." Stimulation of these brain stem nuclei and of the trigeminal complex increases extracranial blood flow by reflex connection with the parasympathetic part of the facial nerve through the greater superficial petrosal nerve and sphenopalatine and otic ganglia. This constitutes a link between neural[2,3] and vascular mechanisms: the "trigeminovascular reflex." Activation of this pathway probably foments a variety of headaches.

Serotonin-1 agonists (such as ergotamine and sumatriptan) bind to receptors and constrict dural and pial vessels. They block the extravasation of plasma in the dura and venous sinuses, which is stimulated by perivascular trigeminal fibres that release neurokinin A, calcitonin G related peptide, and substance P. This important pain mechanism may provide the final common pathway for migraine and other cephalgias, explaining the similarities and overlap between different headache syndromes. Sumatriptan is a specific and selective agonist of serotonin type 1 receptors in cranial blood vessels that causes vasoconstriction. It does not penetrate the blood-brain barrier and has no effects on the central nervous system. The drug has high bioavailability—96% subcutaneously and 14% orally—with peak plasma concentrations at 5-20 minutes.

It is currently available only by subcutaneous injection. Early clinical trials showed relief of headache in 77% of patients at 60 minutes and 83% at two hours, with corresponding improvements in nausea, vomiting, and photophobia.[4] It is also effective in cluster headaches, relieving symptoms at 15 minutes in 74% of patients compared with 26% given placebo.[5] To date, no serious cardiovascular or neurological adverse effects have been reported, though 38% of patients have reported mild transient nausea, vomiting, an odd taste, and flushing and tingling in the head and chest. The subcutaneous preparation will almost certainly be superseded by an oral form, which provides relief in about half to two thirds of attacks within two hours. Second and third attacks respond as well as the first. Comparative trials have shown that sumatriptan is slightly but significantly better than aspirin 900 mg and metoclopramide 10 mg (Legg N, 8th Migraine Trust international symposium, London, 1990).

Goadsby *et al* recently reported a favourable response at two hours in 51% of the patients given oral sumatriptan compared with 9% of those given placebo; rescue medication was needed by 41% of patients taking sumatriptan, but 88% of patients taking placebo.[6] Of 28 patients free of headache at two hours, 11 experienced recurrent headache within 24 hours—a substantial "rebound effect," which may owe more to the natural course of migraine than to a true pharmacological effect.

Sumatriptan seems an effective, safe, and prompt remedy for acute attacks of migraine, suppressing all the symptoms—not just headache—but it does not work in every patient. The present high cost (£41 for two injections) may limit its use to patients prone to unusually refractory, severe, or inconveniently timed attacks. Wider clinical experience is needed before its final place in the treatment of migraine can be defined.

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