# Oral medicine for the General Practitioner: pain

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Some problems encountered by practitioners are common, others rare. The practitioner cannot be expected to diagnose all, but has been trained to recognise oral health and disease, and should be competent to recognise normal variants, and common orofacial disorders. In any case of doubt, the practitioner is advised to seek a second opinion from a colleague. This series is not intended to be comprehensive in coverage either of the conditions encountered, or all aspects of diagnosis or treatment: further details are available in standard texts, in the further reading section, or from the Internet. The present article discusses aspects of pain.

## Pain

Pain in the teeth, mouth, face or head usually has a local cause - often the sequelae of dental caries (odontogenic pain) but, there is the possibility of other disorders causing the pain, such as psychogenic, neurological, vascular and conditions where pain is referred from elsewhere. This article discusses mainly these latter conditions, in which specialist help may be indicated.

The real significance to the patient of orofacial pain (apart from the pain itself) can range from the benign to potentially lethal conditions. Some orofacial pain or headaches have an obvious but relatively unimportant cause (e.g. a hangover - caused mainly by the acetaldehyde resulting from metabolism of alcohol). Others have no obvious underlying organic pathology (and thus termed medically explained symptoms [MUS], e.g. atypical facial pain); some can threaten sight (e.g. giant cell arteritis or benign intracranial hypertension); whereas yet others can be life-threatening organic disorders (e.g. sub-arachnoid haemorrhage, bacterial meningitis, or brain tumours).

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## Local causes of orofacial pain

• *Odontogenic pain*

Most orofacial pain is of course, related to dental disease - odontogenic causes and will not be described further.

• *Mucosal pain*

Pain from oral mucosal lesions can be either localised or diffuse. Localised pain is usually associated with an erosion (a partial thickness loss of epithelium) or ulcer (a full thickness loss of epithelium). Of course, the distinction between these painful conditions can be sometimes difficult or impossible and many patients have both. Diffuse pain may be associated with a widespread infection, mucosal atrophy or erosions or ulceration, or a systemic underlying deficiency disease or other factors, and is usually described as 'soreness' or sometimes 'burning'. Mucosal pain may be aggravated mechanically by touch, or by sour, acidic, spicy, or salty foods, so that few affected patients can tolerate or enjoy citrus fruits or tomatoes for example.

## Other local causes of orofacial pain

• *Jaws*

Pain from the jaws can be caused by direct trauma, infection, malignancies, and Paget's disease but lesions such as cysts, retained roots and impacted teeth are usually painless - unless associated with infection or fracture of the jaw. Malignant tumours usually produce deep, boring pain,

sometimes associated with paraesthesia or anaesthesia but odontogenic and other benign tumours of the bone do not normally produce pain.

• *Salivary glands*

Pain from salivary gland disorders is localised to the affected gland, may be quite severe, and may be intensified by increased saliva production such as before and with meals. Examination usually reveals a swollen tender salivary gland sometimes with a degree of trismus.

• *Sinuses and pharynx*

Disease of the paranasal sinuses and nasopharynx, which can cause oral and/or facial pain, include sinusitis and tumours that can remain undetected until too late.

• *Pressure on mental nerve*

Rarely, pain is caused by pressure from a denture on this nerve.

• *Temporomandibular joint pain*

Pain from the TMJ may result from dysfunction, trauma, inflammation, or tumours. Pain is usually dull, poorly localised, may radiate widely, is usually intensified by movement of the mandible and may be associated with trismus because of spasm in the masticatory muscles. Examination may reveal tender masticatory muscles or occasionally a swollen and warm joint.

Temporomandibular pain-dysfunction syndrome is characterised by pain, clicking and jaw locking or limitation of opening of the jaw. A common disorder, afflicting young women mainly, factors which have been implicated include muscle overactivity (e.g. bruxism, clenching), TMJ disruption and psychiatric history (e.g. anxiety, stressful life events). Precipitating factors may include wide mouth opening, local trauma or emotional upset. Some suggest it to be a psychogenic disorder. Diagnosis is clinical. Most patients recover spontaneously and therefore reassurance and conservative measures are the main management. Practitioners are usually well versed with this problem but recalcitrant cases may need Specialist attention, particularly if simple measures fail.

## Neurological (neuropathic) causes of orofacial pain

Sensory innervation of the mouth, face and scalp depends on the trigeminal nerve. Diseases affecting this nerve can cause orofacial pain or indeed sensory loss - sometimes with serious implications.

Any lesion affecting the trigeminal nerve, whether it be traumatic, cerebrovascular disease, multiple sclerosis, infections such as HIV/AIDS or herpes zoster (for example, post-herpetic neuralgia), inflammatory or neoplastic (for example a nasopharyngeal or antral carcinoma), may cause pain often with physical signs such as facial sensory or motor impairment.

Severe lancinating unilateral orofacial pain may be of idiopathic origin and in the absence of identifiable organic cause is termed idiopathic trigeminal neuralgia. Similar features are seen in the rare idiopathic short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing (SUNCT syndrome).

Trigeminal neuralgia (TN) is an uncommon disorder of the nerve that causes episodes of unilateral intense, stabbing, electric shock-like pain in the areas of the face where the branches of the nerve are distributed - lips, eyes, nose, scalp, forehead, upper jaw, or lower jaw. TN onset is mainly in the 50-70 year age group. The cause is unclear, but one hypothesis is that there may be compression around the trigeminal root in the posterior cranial fossa, possibly due to a cerebral blood vessel becoming atherosclerotic and therefore less flexible with age, and then pressing on the roots of the trigeminal nerve - causing neuronal discharge.

TN has the following main characteristics (International Headache Society):

• Paroxysmal attacks of facial or frontal pain which lasts a few seconds to less than two minutes. These occur especially in the morning, rarely at night

• Pain has at least four of the following characteristics:

i Distribution along one or more divisions of the trigeminal nerve

ii Sudden intense, sharp superficial, stabbing or burning in quality

iii Pain intensity severe

iv Precipitation from trigger areas or by certain daily activities such as eating, talking, washing the face, shaving, or cleaning the teeth

v Between paroxysms, the patient is usually entirely asymptomatic. Some patients experience a dull ache at other times

• No neurological deficit

• Attacks are stereotyped in the individual patient

• Exclusion of other causes of facial pain by history, physical examination and special investigations when necessary.

A less common form of the disorder called 'Atypical Trigeminal Neuralgia' may cause less intense, constant, dull burning or aching pain, sometimes with occasional electric

shock-like stabs. Both forms of the disorder most often affect one side of the face, but some patients experience pain at different times on both sides.

## Diagnosis

TN is universally considered to be one of the most painful afflictions known. Severe pain suggestive of trigeminal neuralgia but with physical signs such as facial sensory or motor impairment can result from cerebrovascular disease, multiple sclerosis, infections such as HIV infection, or space-occupying lesions such as neoplasms. These must therefore be excluded by history, examination (including neurological assessment, especially of cranial nerves) and investigations (including imaging to exclude space-occupying or demyelinating lesions) and blood tests to exclude infections and vasculitides.

## Management

Patients with trigeminal neuralgia are best seen at an early stage by a Specialist in order to confirm the diagnosis and initiate treatment. TN is often an intermittent disease with apparent remissions for months or years but recurrence is common and very often the pain spreads to involve a wider area over time and the intervals between episodes tend to shorten. Few patients have spontaneous remission and thus treatment is usually indicated. Medical treatment is used successfully for most patients, typically using anticonvulsants, especially carbamazepine, which must be given continuously prophylactically for long periods, used carefully and under strict medical surveillance. Adverse effects must be monitored, including:

- Balance (disturbed - ataxia) - this tends to be the feature that limits the dose of carbamazepine
- Blood pressure (may increase) - patients must have a baseline test and then blood pressure estimations for three months, then every six months
- Blood tests - mainly for liver function (may be impaired) and bone marrow function (red and white cells and/or platelets may be depressed).

Other agents are available and some patients report having reduced or relieved pain by means of alternative medical therapies such as acupuncture, chiropractic adjustment, self-hypnosis or meditation.

Should medication be ineffective, or if it produces excessive undesirable side effects, neurosurgical procedures are available to relieve pressure on the nerve or to reduce nerve sensitivity. These can all also produce sensory loss as well as pain relief.

Glossopharyngeal and post-herpetic neuralgias may also cause orofacial pain.

A specialist opinion is warranted to investigate and manage the patients.

## Vascular causes of orofacial pain

Several disorders in which the most obvious organic feature is vascular dilatation or constriction cause orofacial pain. The pain is usually obviously in the face or head rather than in the mouth but occasionally can involve both, and can be difficult to differentiate from other causes or orofacial pain (Table 1). These include:

- Migraine
- Migrainous neuralgia
- Giant cell arteritis.

A rare condition termed neuralgia - inducing cavitational osteonecrosis (NICO), related to disorders in blood coagulation, may also cause jaw pain. A specialist opinion is warranted to investigate and manage the patients.

## Referred causes of orofacial pain

Pain may occasionally be referred to the mouth, face or jaws from the:

- **Neck -** cervical vertebral disease, especially cervical spondylosis, very occasionally causes pain referred to the face
- **Heart** in patients with angina. The pain usually affects the mandible, is initiated by exercise (especially in the cold) and abates quickly on rest
- **Lungs -** orofacial pain emanating from lung cancer is a well-recognised entity
- **Oesophagus -** pain plus sialorrhoea may result from oesophageal lesions
- **Styloid process -** Eagle's syndrome, a rare disorder due to an elongated styloid process (stylalgia), may cause pain on chewing, swallowing or turning the head
- **Eyes -** pain from the eyes can arise from disorders of refraction, retro-bulbar neuritis (for example in multiple sclerosis), or glaucoma, and can radiate to the orbit or frontal region
- **Ears -** middle ear disease may cause headaches. Conversely, oral disease not infrequently causes pain referred to the ear, particularly from lesions of the posterior tongue.
- **Pharynx -** carcinoma of the pharynx may cause facial pain.

A specialist opinion is warranted to investigate and manage the patients.

## Psychogenic causes of orofacial pain

Psychogenic (tension) headaches are common, especially in young adults. The headache, which is caused by anxiety

or stress-induced muscle tension, affects the frontal, occipital and/or temporal muscles, and is felt as a constant ache or band-like pressure. The pain is often worse by the evening, but does not keep the patient awake. Reassurance may be effective but the pain may also be helped by massage, warmth, by non-steroidal anti-inflammatory drugs (NSAIDs), or by benzodiazepines as these are both anxiolytic and mild muscle relaxants, or by complementary therapies. Similar problems can affect the orofacial region.

In some studies, nearly 40% of the population have reported frequent headaches and orofacial pain. The reason behind conditions with a psychogenic component, sometimes termed medically unexplained symptoms (MUS), may include:

- Possible links between neurohumoural mechanisms and altered CNS function
- The heightening of bodily sensations (lowered pain threshold) as a consequence of physiological processes such as autonomic arousal, muscle tension, hyperventilation, or inactivity
- Misattribution of normal sensations to serious physical disorders.

Features common to most MUS include:

- Constant chronic discomfort or pain
- Pain often of a dull boring or burning type
- Pain poorly localised
- Pain may cross the mid-line to involve the other side or may move elsewhere
- Pain which rarely wakens the patient from sleep
- Total lack of objective signs of organic disease
- All investigations are also negative
- There are often recent adverse 'life-events' such as bereavement or family illness
- There are often multiple oral and/or other MUS, such as headaches, chronic back or neck pain, irritable bowel syndrome, insomnia, numbness or dysmenorrhoea
- Cure is uncommon in most, yet few sufferers seem to try or persist using analgesics.

Patients may bring diaries of their symptoms to emphasise their problem. Some have termed this the 'malady of small bits of paper' and though there is by no means always a psychogenic basis, such notes characterise patients with MUS. These days, this is being replaced by internet print-outs, which are also increasingly brought by well-informed patients who have no psychogenic problems whatsoever.

Occasional patients quite deliberately induce painful oral lesions and some have Munchausen's syndrome, where they behave in such a fashion as to appear to want operative intervention.

**Table 1.** Causes of orofacial pain

**Local disorders**

| | |
|---|---|
| Teeth and supporting tissues | Jaws |
| Maxillary antrum | Salivary glands |
| Pharynx | Eyes |

**Neurological disorders**

Idiopathic trigeminal neuralgia
Malignant neoplasms involving the trigeminal nerve
Glossopharyngeal neuralgia
Herpes zoster (including post-herpetic neuralgia)
Multiple sclerosis
Shortlasting, Unilateral, Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT syndrome).

**Possible psychogenic causes**

Atypical facial pain
Burning mouth syndrome
Temporomandibular pain-dysfunction

**Vascular disorders**

Migraine
Migrainous neuralgia
Giant cell arteritis
Paroxysmal hemicrania
Neuralgia-Inducing Cavitational Osteonecrosis (NICO)

**Referred pain**

| | |
|---|---|
| Nasopharyngeal | Ocular |
| Aural | |
| Cardiorespiratory | Angina |
| Lesions in the neck or chest (including lung cancer) | |

**Table 2.** Causes of a burning sensation in the mouth

**Local causes**
Erythema migrans (geographical tongue)
Lichen planus
Candidosis
Denture problems

**Systemic causes**
Psychogenic
Cancerophobia
Depression
Anxiety states
Hypochondriasis
Deficiency of:
- Vitamin B, especially B12
- Folate
- Iron

Dry mouth
Diabetes
Drugs

The most common types of orofacial pain with a strong psychogenic component are
- Oral dysaesthesia (Burning mouth syndrome)
- Atypical facial pain
- Temporomandibular pain-dysfunction
- Atypical odontalgia
- The syndrome of oral complaints

The first two of these are discussed below: the other common complaint, TMJ pain-dysfunction, is often effectively managed in general practice, or by Practitioners with a special interest.

## Burning mouth 'syndrome' (BMS)

Burning mouth 'syndrome' (BMS) - also known as glossopyrosis, glossodynia, oral dysaesthesia or stomatodynia - is the term usually used when symptoms described usually as a burning sensation, exist in the absence of identifiable organic aetiological factors. It is often a medically unexplained symptom (MUS) but it must also be recognised that BMS may well not be a single entity. There may be other causes (Table 2), and a patient in pain may well also manifest psychological reactions to the experience.

BMS is a fairly common chronic complaint, affecting up to 1 person per 20,000 population and seen especially in middle age or elderly patients, particularly in females, in a ratio of about 3:1. There is no specific relationship to hormonal changes, despite the fact that BMS is often seen in middle aged or elderly peri- or post-menopausal females.

Defined clinical conditions that must be excluded since they can also present with burning include
- Erythema migrans (geographic tongue)
- Lichen planus
- Dry mouth
- Candidosis
- Glossitis such as may be associated with haematinic (iron, folic acid, vitamin B) deficiency
- Diabetes.

Uncommon causes that may need to be considered include:
- Hypothyroidism
- Lupus erythematosus
- Mucositis
- Drugs (especially angiotensin-converting enzyme [ACE] inhibitors such as captopril, enalapril, lisinopril; protease inhibitors; cytotoxic agents; clonazepam)
- Hypersensitivity (to sodium metabisulphite, nuts, dental materials and other substances)
- Galvanic reactions to metals in the mouth.

Organic problems that sometimes present with no detectable clinical lesions, but that can cause symptoms similar to BMS include:
- A haematological deficiency state (deficiencies in iron, folic acid or vitamin B) in about 30%
- Restricted tongue space from poor denture construction
- Parafunction such as nocturnal bruxism or tongue-thrusting
- Neuropathy - such as follows damage to the chorda tympani nerve.

No precipitating cause for BMS can be identified in over 50% of the patients, and a psychogenic cause such as anxiety, depression or cancerophobia can be identified in about 20%. In others, BMS appears to follow either:
- Dental intervention or
- An upper respiratory tract infection.

### *Clinical features*

BMS most frequently affects the tongue, but it can also affect the palate or, less commonly, the lips or lower alveolus.

The history is that the burning sensation is chronic, usually bilateral, and often relieved by eating and drinking, in contrast to pain caused by organic lesions which is

typically aggravated by eating. Alcohol may also relieve or reduce the symptoms.

Patients with BMS often have multiple oral and/or other psychogenic related complaints, such as dry mouth, bad or altered taste, thirst, headaches, chronic back pain, irritable bowel syndrome or dysmenorrhoea. There may be changes in sleep patterns and mood and, though patients only uncommonly use analgesics to try and control the symptoms, there have often already been multiple consultations.

Examination shows no clinically detectable signs of mucosal disease or tenderness or swelling of the tongue or affected area, and no neurological or other objective signs. Importantly, all investigations prove negative. Management is discussed below.

## Atypical facial pain (AFP)

Atypical facial pain (AFP) is a constant chronic orofacial discomfort or pain, defined by the International Headache Society as facial pain not fulfilling other criteria. Therefore, like BMS, it is also a diagnosis reached only by the exclusion of organic disease - there are no physical signs, investigations are all negative and it is an MUS. Atypical facial pain is fairly common, probably around 1-2% of the population. Indeed, in some studies, nearly 40% of the population have reported frequent headache and/or orofacial pain.

Atypical facial pain is often of a dull boring or burning type and ill-defined location and there is:

- A total lack of objective signs
- A negative result from all investigations
- No clear explanation as to cause
- Poor response to treatment.

Patients are often middle-aged or older and 70% or more are females. Most sufferers from AFP are otherwise normal individuals who are or have been, under extreme stress such as bereavement, or concerned about cancer. There are often recent adverse life-events, such as bereavement or family illness and/or dental or oral interventive procedures.

Positron emission tomography (PET) studies in persons with AFP have shown enhanced cerebral activity, suggesting an enhanced alerting mechanism in response to peripheral stimuli. This may lead to release of neuropeptides and production of free radicals causing cell damage and release of pain-inducing eicosanoids such as prostaglandins.

### *Clinical features*

History findings include pain mainly in the upper jaw, of distribution unrelated to the anatomical distribution of the trigeminal nerve, poorly localised, and sometimes crossing the mid-line to involve the other side or moving to another site. Pain is often of a deep, dull boring or burning, chronic discomfort, and persists for most or all of the day but does not waken the patient from sleep.

There may also be multiple oral and/or other psychogenic related complaints, such as dry mouth, bad or altered taste, thirst, headaches, chronic back pain, irritable bowel syndrome or dysmenorrhoea. Patients only uncommonly use analgesics to try and control the pain but there is a high level of utilisation of health care services. There have often already been multiple consultations and attempts at treatment.

Pain is accompanied by altered behaviour, anxiety or depression. Over 50% of such patients are depressed or hypochondriacal, and some have lost or been separated from parents in childhood. Many lack insight and will persist in blaming organic diseases (or the dentist!) for their pain.

Examination findings include no tenderness or swelling in the area, no obvious odontogenic or other local cause for the pain, and a total lack of objective physical (including neurological) signs. All imaging studies and blood investigations are negative. Management is discussed below.

## Atypical odontalgia

Atypical odontalgia is pain and hypersensitive teeth in the absence of detectable pathology. The pain is typically indistinguishable from pulpitis or periodontitis but is aggravated by dental intervention. Probably a variant of atypical facial pain, it should be managed similarly. Management is discussed below.

## Diagnosis of orofacial pain

The most important means of diagnosis of orofacial pain is the history (Figure 1). In order to differentiate the widely disparate causes, it is essential to determine key points about the pain:

- Location. Valuable information can be obtained by watching the patient asked if the pain is localised or diffuse. For example, patients frequently point with one finger when describing dental causes or trigeminal neuralgia, but atypical facial pain is much more diffuse, and may radiate
- Character. Patients should be asked about the severity and whether the pain is 'sharp', 'dull', 'aching', 'throbbing' or 'shooting' . Ask the patient to rate the pain severity on

a scale of zero (no pain) to 10 ( most severe pain that the patient has experienced), or ask them to mark this on a line divided into 10 equal sections (visual analogue scale) or use an assessment instrument such as the McGill Pain Questionnaire. These helps assess the severity, accepting always that it is subjective, and may also be useful in monitoring the response to treatment. Disturbance of the normal sleep pattern by pain is also useful in assessing the severity

- Duration. The average duration of each episode may help diagnosis. For example, pain from exposed dentine is fairly transient lasting only for seconds while the pain from pulpitis lasts for a longer period. Trigeminal neuralgia is a brief lancinating pain lasting up to about five seconds - migrainous neuralgia lasts 30 to 45 minutes while atypical facial pain is typically persistent
- Frequency and periodicity. Determine whether the pain occurs at specific times. A pain diary can help. The pain of sinusitis is often aggravated by lying down, while periodic migrainous neuralgia frequently disturbs the patient's sleep at a specific time each night, around 2am. The pain of temporomandibular pain dysfunction syndrome may be more severe on waking
- Precipitating, aggravating and relieving factors. It may be necessary to resort to leading questions. Ask if any factors influence the pain, asking about the effects of temperature, biting, posture, analgesics, alcohol etc.. For example, temperature often aggravates dental pain; touching a trigger zone may precipitate trigeminal neuralgia attacks, stress may worsen atypical facial pain, alcohol may induce migrainous neuralgia episodes
- Associated features. Some types of pain may be associated with other features that are helpful diagnostically, such as a swollen face in dental abscess, nausea and vomiting in migraine, or nasal stuffiness or lacrimation in migrainous neuralgia.

The cause of most orofacial pain is established mainly from the history and examination findings but it is important to consider the usefulness of a Specialist who can arrange additional investigations, particularly imaging of the head and neck, using CT or MRI. It is important not to miss detecting organic disease and thus mislabelling the patient as having psychogenic pain. Various instruments, such as IMPATH and TMJ Scale are available to assess behavioural and psychological factors.

Specialist referral may be indicated if the practitioner feels:

- The diagnosis is unclear
- A serious diagnosis is possible
- Systemic disease may be present
- Unclear as to investigations indicated
- Complex investigations are indicated
- Unclear as to treatment indicated
- Treatment is complex
- Treatment requires agents not readily available
- Unclear as to the prognosis
- The patient would be happier.

Diagnosis of atypical facial pain is clinical through careful examination of the mouth, peri-oral structures, and cranial nerves, and imaging (tooth/jaw/sinus radiography and MRI/CT scan) to exclude organic disease such as space-occupying or demyelinating diseases, are important (Figure 2). Diagnosis of BMS is clinical and oral examination is important to exclude organic causes such as erythema migrans (geographic tongue), candidosis, lichen planus, dry mouth, glossitis, diabetes or denture problems.

Investigations indicated, may include:

- Laboratory screening for excluding
  - i Anaemia, a vitamin or iron deficiency (blood tests)
  - ii Diabetes (blood and urine analyses)
  - iii Thyroid dysfunction (blood analyses)
  - iv Xerostomia (salivary flow rates)
  - v Candidosis (oral rinse)
- Psychological screening using, for example, the Hospital Anxiety and Depression (HAD) scale.

## Management of orofacial pain

It is important where possible, to identify and treat the cause of pain, to relieve factors which lower the pain threshold (fatigue, anxiety and depression) and to avoid polypharmacy.

Simple analgesics such as NSAIDs should be tried initially, before embarking on more potent preparations; chronic pain requires regular analgesia (not just as 'required'). Antidepressants may help in pain of psychogenic origin and anticonvulsants may help in neuropathic pain (neuralgias).

Few patients with atypical facial pain or BMS have spontaneous remission and thus treatment is indicated. Reassurance and attention to any factors such as the dentures or haematinic deficiencies may be indicated, but active dental or oral surgical treatment, or attempts at 'hormone replacement', in the absence of any specific indication, should be avoided. Cognitive-behavioural therapy or a Specialist referral may be indicated. Patient information is a very important aspect in management. A technique termed reattribution helps these patients; it involves demonstrating an understanding of the complaints by taking a history of related physical, mood and social factors, making the patient feel understood and supported, and making the link between the symptoms and psychological problems. It consists of:

• Clearly acknowledging the reality of the patient's symptoms and distress and never attempting to trivialise or dismiss them

• Trying to explain the psychosomatic background to the problem, ascribing the symptoms to causes for which the patient cannot be blamed

• Setting goals which include helping the patient cope with the symptoms rather than attempting any impossible cure

• Not repeating examinations or investigations at subsequent appointments, since this only serves to reinforce illness behaviour and health fears

• Avoiding attempts at relieving pain by operative intervention - since these are rarely successful. Indeed, active dental measures such as restorative treatment, endodontia or oral surgical treatment, in the absence of any specific indication, should be avoided

• Offering referral to a Specialist or a trial of antidepressants, explaining that these agents are being used to treat the symptoms not depression, that some antidepressants have analgesic activity and that antidepressants have been shown in controlled trials to be effective for this problem, even in non-depressed persons. Interestingly, although antidepressants must be given for at least 2-3 weeks to achieve any antidepressive effect, many patients with MUS such as AFP or BMS show symptomatic benefit within one week, suggesting this is not via any antidepressive action.

## Further reading

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